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> (54) NOVEL PENICILLINS AND CEPHALOSPORINS AND PROCESS FOR PRODUCING THE SAME



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(71) We, TOYAMA CHEMICAL CO. LTD., a corporation organised under the laws of Japan, of 1—18, Kayabacho, Nihonbashi, Chuo-ku, Tokyo, Japan, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to novel penicillins and cephalosporins and to a process for producing the same.

The compounds of the present invention have various characteristics including a

The compounds of the present invention have various characteristics including a broad antibacterial spectrum against Gram-positive and Gram-negative bacteria, and effective antibacterial activity particularly against Pseudomonas aeruginosa, Klebsiella pneumoniae and Proteus species. Furthermore, the compounds of the present invention possess high resistance to β -lactamase produced from bacteria, and effective antibacterial activity even against clinical isolates of bacteria which are significant at present from the clinical standpoint. Accordingly, the compounds of the present invention are quite effective as therapeutic drugs for human and animal infectious diseases derived from the above-mentioned pathogenic microorganisms.

It has heretofore been known that 6-acylamino penicillanic acids and 7-acylamino-cephalosporanic acids having an amino group at the α -position of the acyl group show strong antibacterial activity not only against Gram-positive bacteria but also against Gram-negative bacteria. However, there are the disadvantages that the known compounds described above show substantially no effective antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species, which have been known as causes for clinically serious infectious diseases but also resistant bacteria which are frequently isolated at present from many clinical hospitals. And they tend to be hydrolyzed with β -lactamase produced from many drug-resistant bacteria.

With an aim to obtain penicillins and cephalosporins having no disadvantages mentioned above, the present inventors conducted extensive studies to find that novel compounds of formula (I) which appears hereinafter, which are prepared by bonding the moiety.

$$A = N + C = 0$$

$$(R^2 - R^3)_m$$
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wherein A, X, Y, R², R³, n and m are as mentioned hereinafter, to the amino group in the acyl group of penicillins and cephalosporins, can sufficiently satisfy the above-mentioned aim and have extremely valuable therapeutic effects.

It is an object of this invention to provide novel penicillins and cephalosporins containing a mono- or di-oxo- or thioxo-piperazino(thio)carbonylamino group in molecule.

It is another object of this invention to provide novel penicillins and cephalosporins having a broad antibacterial spectrum.

It is a further object of the invention to provide novel penicillins and cephalosporins having high resistance to β -lactamase produced from bacteria.

It is a still further object of the invention to provide novel penicillins and cephalosporins having effective antibacterial activity against clinical isolates of bacteria.

It is a still further object of the invention to provide a process for producing the novel penicillins and cephalosporins.

It is a still further object of the invention to provide a pharmaceutical composition

containing the novel penicillins or cephalosporins as active ingredient.

Other objects and advantages of this invention will become apparent from the fol-

Other objects and advantages of this invention will become apparent from the following description.

The compounds of the present invention are penicillins and cephalosporins represented by the general formula (I),

$$A - N \xrightarrow{3} {}^{2}N - C - NH - R - CONH$$

$$(I)$$

$$(R^{2} R^{3})_{M}^{N}$$

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wherein R represents an amino acid residue; R1 represents a hydrogen atom, an ester-forming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mamalium enzymic action, a silicon-, phosphorus- or tin-containing group which is capable of being easily removed by treatment with H₂O or an alcohol, or a conventional salt-forming cation, n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair om R² and R³ is linked to the same carbon atom, and m pairs of R² and R³, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonylalkyl, acyloxyalkyl, alkoxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R2 and R3 together with a comon carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxyalkyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, carbamoyl, thiocarbamoyl, acylcarbamoyl, acylthiocarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylthiocarbamoyl, sulfamoyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y represents an oxygen or sulfur atom; and

where R' represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio or heterocyclylthio group.

In the above-mentioned general formula (I) R represents an amino acid residue. Examples of such amino acid residue include residues of amino acids derived from various aliphatic, araliphatic, aromatic, alicyclic and heterocyclic compounds, which amino acids may have the amino group at a position such as α -, β - or γ -position to the carboxyl group. Preferable as said R is an α -amino acid residue represented by the formula

wherein R³ is an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl, or cyclohetyl; a cycloalkenyl group such as cyclopentenyl, or cyclohexenyl; a cycloalkadienyl group such as cyclopentadienyl, or cyclohexadienyl; an aryl group such as phenyl or naphthyl; an aralkyl group such as benzyl or phenetyl; an aryloxy group such as phenoxy or naphthoxy; an alkylthioalkyl group such as methylthiomethyl, ethylthiomethyl, methylthioethyl or ethylthioethyl; or a heterocyclic group such as furyl, thienyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, quinazolyl, indolyl, indazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl; each group represented by said R³ may be substituted by various groups, for example, halogen, hydroxy, nitro, alkyl, alkoxy, alkylthio, acyl, or alkylsulfonylamino; R⁶ represents a hydrogen atom; and R³ and R⁶ together with a common carbon atom may form a cycloalkyl ring such as cyclohexyl or cyclohexyl; a cycloalkenyl ring such as cyclopentadienyl or cyclohexadienyl.

In the general formula (I), R1 is a hydrogen atom, a blocking group or a salt-forming cation. The blocking group may be any of those which have heretofore been

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used in the field of penicillin or cephalosporin type compounds. Concretely, the blocking group includes (1) ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions e.g. arylsulfonylalkyl groups such as toluene-sulfonylethyl, substituted or unsubstituted aralkyl groups such as benzyl, 4-nitrobenzyl, diphenylmethyl, trityl and 3,5-di(tert.-butyl)-4-hydroxy-benzyl; substituted or unsubstituted alkyl groups such as tert.-butyl, trichloroethyl, phenacyl groups; alkoxyalkyl groups such as methoxymethyl; and unsubstituted or alkyl-substituted cyclic aminoalkyl groups such as piperidinoethyl, 4-methylpiperidinoethyl, morpholinoethyl or pyrrolidinoethyl, (2) ester-forming groups capable of being easily removed owing to enzymes in a living body, e.g. acyloxyalkyl groups such as pivaloyloxymethyl; phthalide group; and indanyl group; (3) silicon-containing groups, phosphorus-containing groups and tin-containing groups which are capable of being easily removed by treating with H₂O or an alcohol, such as

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$$(CH_3)_3 Si -$$
, $\begin{bmatrix} 0 & C_2H_5O \\ O & C_2H_5O \end{bmatrix} P -$, or $(C_4H_9)_3 Sn -$,

The examples of the blocking groups mentioned in above (1), (2) and (3) are merely typical, and other examples are disclosed in U.S. Patents 3,499,909; 3,573,296 and 15 3,641,018 and DOS 2,301,014; 2,253,287 and 2,337,105 and may be used in this invention. The salt-forming cation includes conventional cations which have heretofore been known in the field of penicillin or cephalosporin type compounds, ad preferable are those capable of forming non-toxic salts. The salts include alkali metal salts such as 20 the sodium salt or the potassium salt; alkaline earth metal salts such as the calcium salt or the magnesium salt; ammonium salt; and salts with nitrogen-containing organic bases such as procaine, dibenzylamine, N-benzyl-\(\beta\)-phenethylamine, 1-ephenamine, or N,N-dibenzylethylenediamine. In addition to the above cations, there may be used 25 cations capable of forming the salts with other nitrogen-containing organic bases, such as trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiper-idine, N-methylmorpholine, diethylamine, or dicyclohexylamine. Furthermore, the cation includes quaternary ammonium groups formed at the 3-position of cephem ring, such as pyridinium, quinolinium, isoquinolinium and pyrimidinium. In this case, a betaine structure is formed in the molecule. 30

In the general formula (I), m pairs of R² and R³, which may be the same or different, represent individually, a hydrogen atom; a halogen atom such as fluorine, chlorine or bromine; a carboxyl group; an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; an aryl group such as phenyl or naphthyl; an acyl group such as acetyl, propionyl, butyryl or benzoyl; an aralkyl group such as benzyl or phenethyl; an alkoxycarbonylalkyl group such as methoxycarbonylmethyl or ethoxycarbonylmethyl; an acyloxyalkyl group such as acetyloxymethyl, propionyloxymethyl, pivaloyloxymethyl or benzoyloxymethyl; an alkoxy group such as methoxy, ethoxy, propoxy or butoxy; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl; a cycloalkyloxycarbonyl group such as cyclopentyloxycarbonyl, cyclohexyloxycarbonyl or cycloheptyloxycarbonyl; an aralkoxycarbonyl group such as benzyloxycarbonyl or phenethoxycarbonyl; an aryloxycarbonyl group such as phenoxycarbonyl or naphthoxycarbonyl; an amino group such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino or N-butylamino), N-acylamino (e.g. N-memylamino, N-emylamino, N-diethylamino or N,N-diethylamino), N-acylamino (e.g. N-acetylamino, N-propionylamino, N-butyrylamino or N-benzoylamino), and cyclic amino (e.g. pyrrolidino, piperidino, or morpholino); and a carbamoyl group such as carbamoyl N-methylaminocarbonyl, N-ethylaminocarbonyl, N,N-dimethylaminocarbonyl or N,N-diethylaminocarbonyl. Further, R² and R³ together with a common carbon atom may form a cycloalkyl ring such as a cyclopentyl, cyclohexyl or cycloheptyl group. Each of the groups mentioned above for said R2 and R3 may be substituted by various substituents, for example, halogen atoms, or alkyl, alkoxy, alkylthio, acyl or nitro groups.

In the general formula (I), A represents a hydrogen atom; a hydroxy group; a

nitro group, a cyano group; an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, or dodecyl; an alkenyl group such as vinyl, propenyl or butenyl; an alkynyl group such as propargyl; an alkadienyl group such as 1,3-butadienyl or 1,3-pentadienyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; a cycloalkenyl group such as cyclopentenyl or cyclohexenyl; a cycloalkadienyl

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	group such as cyclopentadienyl or cyclohexadienyl; an aryl group such as phenyl or naphthyl; an acyl group such as formyl, acetyl, propionyl, isovaleryl, caproyl, enanthoyl, capryloyl, palmitoyl, stearoyl, acryloyl, cyclohexanecarbonyl, benzoyl, phenylglycyl,	
7	furoyl or thenoyl; an aralkyl group such as benzyl or phenethyl; an acyloxyalkyl group such as acetyloxyethyl, pivaloyloxymethyl or benzoyloxymethyl; an alkoxy group such	5
.5	as methoxy, ethoxy, propoxy or butoxy; a cycloalkyloxy group such as cyclopentyloxy,	3
	cyclohexyloxy or cycloheptyloxy; an aryloxy group such as phenoxy or naphthoxy; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or	
	butoxycarbonyl: a cycloalkyloxycarbonyl group such as cyclopentyloxycarbonyl, cyclo-	40
10	hexyloxycarbonyl, or cycloheptyloxycarbonyl; an aryloxycarbonyl group such as phenoxycarbonyl or (1- or 2-)naphthoxycarbonyl; an aralkoxycarbonyl group such as benz-	10
	yloxycarbonyl or phenethoxycarbonyl; an alkylsulfonyl group such as methanesulfonyl, ethanesulfonyl, propanesulfonyl or butanesulfonyl; a cycloalkylsulfonyl group such as	
	cyclopentanesulfonyl or cyclohexanesulfonyl; an arylsulfonyl group such as benzene-	
15	sufonyl or (1- or 2-)naphthalenesulfonyl; a carbamoyl group such as carbamoyl, N-alkylaminocarbonyl (e.g. N-methylaminocarbonyl, N-ethylaminocarbonyl, N-propyl-	15
	aminocarbonyl or N-butylaminocarbonyl), N-arylaminocarbonyl (e.g. N-phenylamino-	
-	carbonyl), N,N-dialkylaminocarbonyl (e.g. N,N-dimethylaminocarbonyl or N,N-diethylaminocarbonyl), cyclic amino carbonyl (e.g. pyrrolidinocarbonyl, piperidino-	
20	carbonyl or morpholinocarbonyl); a thiocarbamoyl group such as thiocarbamoyl, N-	20
20	alkylaminothiocarbonyl (e.g. N-methylaminothiocarbonyl, N-ethylaminothiocarbonyl or	
	N-propylaminothiocarbonyl), N-arylaminothiocarbonyl (e.g. N-phenylaminothiocarbonyl), N,N-dialkylaminothiocarbonyl (e.g. N,N-dimethylaminothiocarbonyl or	
	N.N-diethylaminothiocarbonyl), or cyclic aminothiocarbonyl (e.g. pyrrolidinothio-	
25	carbonyl, piperidinothiocarbonyl or morpholinothiocarbonyl); an acylcarbamoyl group such as N-acetylcarbamoyl, N-propionylcarbamoyl, N-butyrylcarbamoyl, N-benzoyl-	25
	carbamovl, N-furovicaramovl, or N-thenovicarbamovl; an acylthiocarbamovl group	
	such as N-acetylthiocarbamoyl, N-propionylthiocarbamoyl, N-butyrylthiocarbamoyl,	
30	N-benzoylthiocarbamoyl, N-naphthoylthiocarbamoyl, N-furoylthiocarbamoyl or N-thenoylthiocarbamoyl); an alkylsulfonylcarbamoyl group such as methanesulfonylamino-	30
30	carbonyl, ethanesulfonylaminocarbonyl or butanesulfonylaminocarbonyl; an arylsulfonyl-	
-	carbamoyl group such as benzenesulfonylaminocarbonyl or (1- or 2-)naphthalenesulfonylaminocarbonyl; an alkylsulfonylthiocarbamoyl group such as methanesulfonyl-	
	aminothicarbonyl, ethanesulfonylaminothicarbonyl or butanesulfonylaminothicarb-	25
35	onyl; an arylsulfonylthiocarbamoyl group such as benzenesulfonylaminothiocarbonyl or naphthalenesulfonylaminothiocarbonyl; a sulfamoyl group such as sulfamoyl, N-methyl-	35
	sulfamovi. N-ethylsulfamovi. N-propylsulfamovi. N-butylsulfamovi, N,N-dimethylsulf-	
	amoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibtuylsulfamoyl, N-phenylsulfamoyl, N-benzylsulfamoyl, N-cyclopentylsulfamoyl or N-cyclohexylsulf-	
40	amovi: an alkoxycarbonyithioalkyl group such as methoxycarbonyithiomethyl, ethoxy-	40
	carbonylthiomethyl, propoxycarbonylthiomethyl, butoxycarbonylthiomethyl or methoxycarbonylthioethyl; an alkoxythiocarbonylthioalkyl group such as methoxythiocarbonylthioalkyl group such as methoxythiocarbonylthioalkyl	
	onvirthiomethyl, ethoxythiocarbonylthiomethyl, propoxythiocarbonylthiomethyl, butoxy-	
	thiogarbonylthiomethyl or methoxythiocarbonylthioethyl; an amino group such as	45
45	amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino or N-butylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or N,N-	
•	dibutylamino), N-acylamino (e.g. N-acetylamino, N-propionylamino, N-butyrylamino	
	or N-benzoylamino), or cyclic amino (e.g. pyrrolidino, piperidino or morpholino); or a heterocyclic group such as thiazolyl, pyridyl, pyridazyl, pyrazyl, thiadiazolyl, triazolyl,	
50 -	tetrazolyl or quinolyl. Each of the groups mentioned above for A in formula (I) may	50
	be substituted by any of such substituents as, for example, halogen atoms, hydroxyl groups, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, amino	
è	groups (e.g. dialkylamino or cyclic amino), carboxyl groups and acyl groups.	
. •	The quaternary ammonium groups for R ⁴ include pyridinium, quinolinium, iso-quinolinium and pyrimidinium. Further, the organic group which is linked through O,	55
_ 55	N or S for R4 includes alkoxy groups such as methoxy, ethoxy or propoxy; aryloxy	-
	groups such as phenoxy or naphthoxy; aralkoxy groups such as benzyloxy or phenethoxy; acyloxy groups such as acetyloxy, propionyloxy, butyryloxy, benzoyloxy, naph-	
	thovloxy, evelopentanecarbonyloxy, cyclohexanecarbonyloxy, furoyloxy or thenoyloxy;	
60	carbamoyloxy groups such as carbamoyloxy, N-methylaminocarbonyloxy, N,N-	60
	benzylaminocarbonyloxy or cyclohexylaminocarbonyloxy; guanidino groups such as	
	manidino or N-methylmanidino; amino groups such as amino, N-alkylamino (e.g. N-	
65	methylamino, N-ethylamino, N-propylamino, N-butylamino, N-cyclohexylamino or N-phenylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or	65
UJ.		

N,N-dibutylamino), and cyclic amino (e.g. pyrrolidino, piperidino or morpholino); alkylthio groups such as methylthio, ethylthio or propylthio; arylthio groups such as phenylthio or (1- or 2-)naphthylthio; aralkylthio groups such as benzylthio or phenethylthio; acylthio groups such as acetylthio, propionylthio, butyrylthio, benzoylthio, (1- or 2-)naphthoylthio, cyclopentanecarbonylthio, cyclohexanecarbonylthio, furoylthio, thenoylthio, isothiazolecarbonylthio, isoxazolecarbonylthio, thiadiazolecarbonylthio or triazolecarbonylthio; thiocarbamoylthio groups such as thiocarbamoylthio, N-methylthiocarbamoylthio, norpholinothiocarbonylthio or 4-methyl-1-piperazinothiocarbonylthio; alkoxythiocarbonylthio groups such as methoxythiocarbonylthio, ethoxythiocarbonylthio, propoxythiocarbonylthio or butoxythiocarbonylthio; aryloxythiocarbonylthio groups such as phenoxythiocarbonylthio; cycloalkyloxythiocarbonylthio groups such as cyclohexyloxythiocarbonylthio; amidinothio groups such as amidinothio, N-methylamidinothio or N,N'-dimethylamidinothio; and heterocyclic thio groups such as oxazolylthio, thiazolylthio, isoxazolylthio, isothiazolylthio, imidazolylthio, pyriazinylthio, pyrimidinylthio, oxadiazolylthio, quinolylthio, pyrazolylthio, pyriazinylthio, benzimidazolylthio, benzomazolylthio, triazolylthio, triazolypridylthio, purinylthio, pyridine-1-oxide-2-ylthio or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for R⁴ may be substituted by any of such substituents as, for example, halogen atoms, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, acylamino groups, acyl groups, carboxyl groups or carbamoyl groups.

The above-mentioned compounds of formula (I) of the present invention have

The above-mentioned compounds of formula (I) of the present invention have their optical isomers, and all of D-isomers, L-isomers and racemic compounds thereof

are involved in the scope of the present invention.

In the present invention, preferable compounds of the general formula (I) are as follows:

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are as defined above.

The compounds of formula (I) of the present invention are produced according to either the process (1), (2) or (3) described below.

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Process (1):

A process comprising reacting a compound represented by the general formula (II),

$$R^7-NH-R-CONH$$

$$0$$

$$COOR_1$$
(II)

10 with a reactive derivative in the

_с_он

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group (hereinafter refered to as "(thio)carboxyl group") of a compound represented by the general formula (III),

$$A - N = N - C - OH$$

$$(III)$$

Process (2):
A process comprising reacting a compound represented by the general formula (IV),

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with a compound represented by the general formula (V),

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$$A = N + C = NH - R - C = OH$$
 (V)

or with a reactive derivative in the

_C_OH

group (hereinafter referred to as "carboxyl group") of the compound of formula (V).

Process (3):
A process comprising reacting a compound represented by the general formula
(VI),

$$A - N = \begin{pmatrix} (X)_n \\ N - C \\ V \end{pmatrix} - NH - R - CONH$$

$$(VI)$$

$$(R^2 R^3)_m$$

$$(VI)$$

	R ⁰ M (VII) or with a tertiary amine.		Ä
5	In the above-mentioned formulas (II) to (VI), R, R ¹ , R ² , R ³ , R ⁴ , X, m, n, A, Y and	≂ 5∵	
3	anu \	٠,	Ž
	, z		
	are as defined above; and R7 represents a hydrogen atom, a silicon-containing group or		
10	a phosphorus-containing group, these silicon-containing and phosphorus-containing groups having the same meanings as mentioned above for R ¹ . In the aforesaid formula (VI), B represents a substituent capable of being easily replaced by a nucleophilic reagent, and includes, for example, halogen atoms such as chlorine or bromine; lower alkanoyloxy groups such as formyloxy, acetoxy, propionyloxy, butyryloxy or pivaloyloxy; arylcarbonyloxy groups such as benzoyloxy or naph-	10	
15	thoyloxy; arylcarbonylthio groups such as benzoylthio or naphthoylthio; carbamoyloxy groups; heteroaromatic amine N-oxide thio groups having a thio-group on the carbon atom adjacent to the N-oxide group in the molecule, such as pyridine-1-oxide-2-ylthio	15	
20	or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for B may be substituted by any of such substituents as, halogen atoms, nitro groups alkyl groups, alkoxy groups, alkylthio groups or acyl groups. In formula (VII), R ⁸ represents a cyano group, an azido group or an organic group linked through O, N or S, and this organic group is the same as mentioned above	20	
25	for R ⁴ . In the formula (VII), M represents a hydrogen atom, an alkali metal or an alkaline earth metal. The tertiary amine used in the process (3) includes pyridine, quinoline, isoquinoline or pyrimidine. These tertiary amines may be substituted by various substituents such as halogen, lower alkyl or carbamoyl. As the compound (II), there may be used any of D-isomer, L-isomer or racemic	25	
30	compound. As the reactive derivative of the (thio)carboxyl group of the compound of formula (II), there is used a reactive derivative of a carboxylic acid which is ordinarily employed for the synthesis of acid amide compounds. Examples of the reactive deriva-	30	
35	tive are acid halides, acid azides, acid cyanides, mixed acid anhydrides, active esters or active amides. Particularly preferable examples thereof are acid halides such as acid chlorides or acid bromides, and active esters such as cyanomethyl ester or trichloromethyl ester.	35	
40	The reactive derivative of the (thio)carboxyl group of the compound of formula (III) can be easily obtained by reacting, for example, an oxopiperazine or thioxopiperazine of formula (VIII) synthesized according to the process of the literature references described below, with phosgene, thiophosgene, or trichloromethyl ester of chloroformic acid,	40	
70			
	$\begin{array}{c} (X)_{n} \\ A-N \\ (R^{2} \\ R^{3})_{m} \end{array}$		
	wherein A, X, R ² , R ³ , m and n are as defined previously.		ē.
45	Literature references: V. G. Granik, Khim-Farm. Zh., I(4), 16—19 (1967) (Russ); Samuel R. Aspinall, J. An. Chem. Soc., 62, 1202—4 (1940); Kuniyoshi MASUZAWA, Pharm. Bull. (Japan), 38 2078—2081 (1966);	± 45	*
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50	Patric T. Izzo, J. Am. Chem. Soc., 81 4668—4670 (1959); and B. H. Chase & A. M. Downes, J. Chem. Soc., 3874—3877 (1953). Concrete examples of the compound of formula (VIII) and the reactive derivative of (thio)carboxyl group of the compound of formula (III) are as set forth in Table 1 and Table 2, respectively, but it is needless to say that these are not limitative.	50	
	•		

Table 1

Compound	m.p. (recry- stallization solvent)	IR (cm ⁻¹)
O HN_NH	136°C ((⁰ ₀))	$V_{C=0}$ 1640 V_{NH} 3450 - 3250
O CH3 HN NH	b.p. 143 ^o C/l mmHg oily material	$ \sqrt{\frac{1650}{NH}} $ 3300 - 3200
O HN NH CH ₃	b.p. 122 - 125°C/2 mmHg 140 - 141°C (IPA)	$ \sqrt[4]{_{C=0}} $ 1650 - 1630 $ \sqrt[4]{_{NH}} $ 3260, 3170
O CH ₃ HN NH CH ₃	85 - 86 ⁰ C (IPA - IPE)	ν _{C=0} 1660 - 1620
O CH ₂ CO ₂ C ₂ H ₅ HN NH	105 - 106 ⁰ C (Ac0Et)	$ \lambda_{C=0} $ 1710, 1640 $ \lambda_{NH} $ 3300, 3190
CH3CON NH	112 - 113°C (((()))	$V_{C=0}$ 1645, 1625 V_{NH} 3380, 3220
C1CH2CON NH	129 - 130 ⁰ C (IPA)	$y_{C=0}$ 1650, 1630 y_{NH} 3270

- cont'd

Table 1 (Cont'd)

C12CHCON NH	134 - 135°C (IPA)	ν _{C=0} 1660-1630 ν _{NH} 3280
CH ₃ (CH ₂) ₁₃ CH ₂ CON NH	96 - 97°C (CC1 ₄)	ν _{C=0} 1670, 1640 · ν _{NH} 3200
CH ₃ (CH ₂) ₅ CH ₂ CON NH	80 - 81 ⁰ C (IPE)	ν _{C=0} 1660, 1620 ν _{NH} 3250
CH ₃ (CH ₂) ₄ CH ₂ CON NH	83 - 84°C (IPE)	ν _{C=O} 1660, 1620 ν _{NH} 3250
CH3(CH2)3CH2CON NH	99 - 100°C (CC1 ₄)	ν _{C=0} 1660, 1620 ν _{NH} 3250
H CON NH	203 - 205 ⁰ C (IPA)	γ _{C=0} 1670, 1620 γ _{NH} 3250
O CON NH	91 - 93 ⁰ C (IPA)	√ _{C=0} 1640, 1600 √ _{NH} 3250
c1-(O)-con nh	146 - 148 ⁰ C (IPA)	√ _{C=0} 1650, 1620 √ _{NH} 3200
ch3-(O)- con nh	118 - 120 ⁰ C (IPA)	Υ _{C=0} 1660, 1620 Υ _{NH} 3200
CH ₃ O O O CH ₃ O O CH ₃ O	182 - 185 ⁰ C (IPA)	ν _{C=0} 1670, 1600 ν _{NH} 3200

Table 1 (Cont'd)

C1 O NH	Oily material	ν _{C=O} 1650, 1620 ν _{NH} 3200
CH3 O CH3CON NH	124 - 126°C (O)	ν _{C=0} 1650, 1630 ν _{NH} 3225
O CH3SO2N NH	167 - 168°C (EtOH)	$V_{C=0}$ 1680 V_{NH} 3200 $V_{SO_2N<}$ 1310, 1140
CH3CONHCON NH	176 - 179°c (O)	ν _{C=0} 1680, 1650, 1620 ν _{NH} 3300
O-nhcon nh	85 - 88°C (AcOEt)	$V_{C=0}$ 1660, 1640 V_{NH} 3300, 3200
CH3CH2OCON NH	81 - 82°C ((°))	$v_{C=0}$ 1690 - 1650 v_{NH} 3200, 3050
Сн3)3СО-ОСН2-N NH	189 - 190°C (IPA)	$V_{C=0}$ 1650, 1620 V_{NH} 3250
o O HN NH	136 - 138 ⁰ C (Acetone)	γ _{C=O} 1660 γ _{NH} 3200
CH ₃ (CH ₂) ₄ CH ₂ -N NH	Oily material	ν _{C=0} 1650 - 1630 ν _{NH} 3270
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	V _{NH} 3250 V _{C=0} 1650 - 1630

Table 1 (Cont'd)

	· · · · · · · · · · · · · · · · · · ·	
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1650 - 1620
CH ₃ (CH ₂) ₆ CH ₂ -NNH	Oily material	V _{NH} 3270 V _{C=0} 1650 - 1630 Hydrochloride V _{C=0} 1680 V _{NH} 3200, 3080
CH3CON NH	Oily material	ν _{C=0} 1680 ν _{NH} 3300
O-NHCON NH	Oily material	$V_{\rm C=0}$ 1720, 1640 $V_{\rm NH}$ 3300
CH3N NH	b.p. 104 ⁰ C/4 mmHg	√ _{C=0} 1620 √ _{NH} 3275
CH ₃ CH ₂ -N NH	Oily material	√ _{C=0} 1610 √ _{NH} 3250
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1610 ν _{NH} 3250
о (сн ₃) ₂ сн-и ин	Oily material	V _{C=0} 1610 V _{NH} 3400 - 3200
CH ₃ (CH ₂) ₃ CH ₂ -N NH	Oily material	ν _{C=0} 1620 ν _{NH} 3270
CH ₃ CHCH ₂ CH ₂ -N NH	Oily material	$V_{\rm C=0}$ 1620 $V_{\rm NH}$ 3270

- cont'd

Table 1 (Cont'd)

I		
CH ₃ (CH ₂) ₄ CH ₂ -N NH	Oily material	ν _{C=0} 1620 ν _{NH} 3270
сн ₃ (сн ₂) ₅ сн ₂ -и ин	Oily material	ν _{C=0} 1620 ν _{NH} 3270
CH3(CH5)6CH5-N NH	Oily material	ν _{C=0} 1620 ν _{NH} 3270
о сн ₃ (сн ₂) ₁₀ сн ₂ -и ин	Oily material	ν _{C=0} 1620 ν _{NH} 3270
H)—N NH	Oily material	√ _{C=0} 1620 √ _{NH} 3300
O CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	√ _{C=0} 1630 √ _{NH} 3300
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	√ _{C=0} 1630 √ _{NH} 3300
CH ₃ (CH ₂) ₂ CH ₂ -N NH CH ₃	Oily material	ν _{C=0} 1630 ν _{NH} 3200
O-CH2-N NH	157 - 158°c ([°])	ν _{C=0} 1630 ν _{NH} 3300

Table 1 (Cont'd)

		هِ
O CH ₃ H ₂ NCO-N NH	Oily material	$V_{C=0}$ 1700 V_{NH} 3400 - 3250
HOCH ₂ CH ₂ -N NH	b.p. 183- 185°C/2mmHg	V _{C=0} 1620
CH ₂ =CHCH ₂ -N NH	Oily material	V _{C=0} 1650 V _{NH} 3300
CH ₂ =CHCH-N NH CH ₃	Oily material	ν _{C=0} 1620 ν _{NH} 3300
CH ₂ =CCH ₂ -N NH CH ₃	Oily material	ν _{C=0} 1640 ν _{NH} 3300
CH=CHCH ₂ -N NH I CH ₃	Oily material	V _{C=0} 1660 V _{NH} 3350
O NCH ₂ -N NH	Oily material	ν _{C=0} 1630 ν _{NH} 3300
CH3CO-N NH	184 - 185 ⁰ C (EtOH)	$V_{C=0}$ 1690 - 1650 V_{NH} 3190, 3050
O-con nh	177 - 178 ⁰ C (EtoH)	$V_{C=0}$ 1680 - 1650 V_{NH} 3190, 3050

- contid.

Table 1 (Cont'd)

CH ₃ -N NH	142 - 143°C (IPA)	ν _{C=0} 1680 - 1620 ν _{NH} 3200
O-ch ₂ -N-NH	209°C (IPA)	$V_{\rm C=0}$ 1660 - 1630 $V_{\rm NH}$ 3230
O O CH3-N NH	158 ⁰ C (IPA)	V _{C=0} 1695, 1660 V _{NH} 3220
O O CH3COOCH2CH2-N NH	Oily material	$V_{C=0}$ 1730 - 1650 V_{NH} 3300 - 3200
O O CH3CH2-N NH	124°C ((0))	$V_{C=0}$ 1680, 1650 V_{NH} 3250
CH3CH2CH2-N NH	98 - 100°c ((°))	$V_{\rm C=0}$ 1680, 1650 $V_{\rm NH}$ 3200, 3100
0 0 сн ₃ (сн ₂) ₂ сн ₂ -и ин	111 - 113°C (CCl ₄)	$\sqrt{\frac{1695, 1670}{NH}}$ 3240, 3150
о о (сн ₃) ₂ сн-и мн	166 - 167°C ((0))	ν _{C=0} 1650 ν _{NH} 3300 - 3200
0 0 У—(СН ₃ (СН ₂) ₃ СН ₂ -N_NH	104 - 106°C (IPE)	$V_{\rm C=0}$ 1700, 1660 $V_{\rm NH}$ 3200, 3100
0 0 СН ₃ (СН ₂) ₄ СН ₂ -N_NH	111 - 115°C (IPE)	V _{C=0} 1700, 1660 V _{NH} 3200, 3100

Table 1 (Cont'd)

		<u> </u>
CH ₃ (CH ₂) ₅ CH ₂ -N NH	112 - 115 ⁰ C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3200, 3100
CH ₃ (CH ₂) ₆ CH ₂ -N NH	116 - 120°C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3225, 3100
O O CH ₂ =CHCH ₂ -N NH	136 - 137 ⁰ C (Acetone)	$V_{C=0}$ 1680, 1655 V_{NH} 3200, 3100
O O NH	202 - 204 ⁰ C (IPA)	ν _{C=0} 1690, 1645 ν _{NH} 3260
O O C1CH ₂ CH ₂ N NH	128 - 129 ⁰ C (EtOH)	$V_{C=0}$ 1700 – 1650 V_{NH} 3200 – 3100
O O CH3CH2-N NH CH3	127 - 128 ⁰ C (Ac0Et)	ν _{C=O} 1660 ν _{NH} 3200, 3080
O O CH3-N NH CH3	146 - 147°C ((<mark>0</mark>))	$V_{C=0}$ 1660 V_{NH} 3200, 3100
O H NH	183 — 185 ⁰ С (ЕtОН)	ν _{C=0} 1720, 1660 ν _{NH} 3320, 3175, 3050
O-cH ₂ -N NH	96 - 99°C (IPA-n-Hexane)	ν _{C=0} 1720, 1660 ν _{NH} 3330

Table 1 (Cont'd)

C13CCH2OCO-N NH	143 - 146 ⁰ C (IPA)	ν _{C=0} 1765, 1720, 1680 ν _{NH} 3350
O HN NH O	210 - 212 ⁰ C (MeOH)	$\sqrt{c}_{=0}$ 1680 \sqrt{c}_{NH} 3380, 3290, 3070
O CH ₃ HN NH	132 - 133°C (EtOH)	$V_{C=0}$ 1715, 1685 V_{NH} 3275, 3170
OCH ₂ -N NH	98 - 100°C (IPA)	V _{C=0} 1715, 1665 V _{NH} 3360

Note: IPA = $(CH_3)_2CHOH$

IPE = (CH₃)₂CHOCH(CH₃)₂

AcOEt = CH3COOCH2CH3

EtOH = CH3CH2OH

Table 2

Reactive derivatives of A-N N-COH (III)
$$(R^2R^3)_m$$

Compound	Physical property	I.	R. (cm ⁻¹)
о сн ₃ со-и_и-сос1	Oily material	ν _{C=0}	1790, 1710, 1640
O Clch ² CO-N N-COCl	n .	ν _{c=0}	1790, 1730 – 1650
C12CHCO-N N-COC1	11	√ _{C=0}	1790, 1730 - 1650
о сн ₃ (сн ₂) ₁₃ сн ₂ со-и и-сос	;ı " [λ _{C=0}	1740, 1660, 1640
CH ₃ (CH ₂) ₅ CH ₂ CO-N N-COCI	11	V _{C=0}	1740, 1680 - 1640
CH ₃ (CH ₂) ₄ CH ₂ CO-N_N-COC	. 11	√ _{C=0}	1740, 1680 - 1640
CH ₃ (CH ₂) ₃ CH ₂ CO-N N-COC1		$V_{C=0}$	1790, 1710, 1640

Table 2 (Cont'd)

(H)-co-n n-cocl	Oily material	ν _{C=0} 1790, 1730,
O-co-n n-coc1	11	ν _{C=0} 1740, 1660, 1630
0 c1<0>-c0-n_n-c0c1	tr .	ν _{C=0} 1740, 1640
о сн ₃ -{О}- со-ии-сос1		V _{C=0} 1730, 1650
сн ₃ 0 о сн ₃ 0 со-и и-сос1	11	√ _{C=0} 1740, 1640
c1 O COC1		√ _{C=0} 1720, 1640
CH ₃ O CH ₃ CO-N N-COC1	н	Υ _{C=0} 1790, 1710,
o ch ₃ so ₂ -n n-coc1		$ \sqrt[4]{c_{=0}} $ 1790, 1700 $ \sqrt[4]{so_2} $ 1320, 1140
CH3CONHCO-N N-COCI	11	V _{C=0} 1790, 1720 - 1660

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Table 2 (Cont'd)

	·	
O-NHCO-N N-COCI	Oily material	ν _{C=0} 1740, 1720, 1650
CH3CH2OCO-N N-COC1	11	ν _{C=0} 1750, 1720,
о (сн ₃) ₃ ссоосн ₂ -и и-сос1	11	√ _{C=0} 1740 - 1720, 1670
CH ₃ (CH ₂) ₄ CH ₂ -N N-COC1	11	√ _{C=0} 1790, 1720
CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	11	√ _{C=0} 1790, 1720
CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	11	ν _{C=0} 1790, 1720
CH ₃ (CH ₂) ₆ CH ₂ -N N-COC1	11	ν _{C=0} 1790, 1720
O N-COC1	m.p. 115 - 116°C (decomp.) (from ())	ν _{C=0} 1720, 1660
O CH ₃ HN N-COC1 CH ₃	Crystal	√ _{C=0} 1730, 1670

Table 2 (Cont'd)

	•	
O HN_N-COC1 CH ₃	Crystal	√ _{C=0} 1720, 1660
O CH ₂ COOCH ₂ CH ₃ HN N-COC1	m.p. 59 - 60 ⁰ C (from IPE)	ν _{C=0} 1710 - 1730,
O CH ₃	m.p. 98 - 100°C (from ())	ν _{C=0} 1725, 1650
O CH ₃ CH ₃ CO-N N-COC1	Oily material	√ _{C=0} 1720, 1690
O-NHCO-N N-COC1	n	ν _{C=0} 1790, 1740 - 1700
CH3-N N-COCI	ri .	ν _{C=0} 1710, 1630
о сн ₃ (сн ₂) ₂ сн ₂ -и и-сосі	17	ν _{C=0} 1730, 1650
CH ₃ CH ₂ -N N-COC1	11	ν _{C=0} 1730, 1650
O (CH ₃) ₂ CH-N N-COC1	11	√ _{C=0} 1720, 1640

Table 2 (Cont'd)

Oily material	√ _{C=0} 1730, 1640
II	ν _{C=0} 1720, 1640
n .	V _{C=0} 1730, 1640
tt ·	√ _{C=0} 1730, 1640
11	√ _{C=0} 1720, 1640
н	ν _{C=0} 1720, 1640
11	Υ _{C=0} 1730, 1640
11	√ _{C=0} 1730, 1640
tt	√ _{C=0} 1720, 1640
	11

Table 2 (Cont'd)

CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	Oily material	γ _{C=O} 1730, 1650
O O HN N-COCI	m.p. 105 - 107°C	V _{C=0} 1730, 1650
O CH ₂ -N N-COC1	Oily material	ν _{C=0} 1720, 1645
O CH ₃ H ₂ NCO-N N-COC1		√ _{C=0} 1700 - 1740
O HOCH ₂ CH ₂ -N N-COC1	II ,	√ _{C=0} 1730, 1660 - 1630
O CH ₂ =CHCH ₂ -N N-COC1	11	√ _{C=0} 1720, 1640
CH ₂ =CHCH-N N-COC1	11	√ _{C=0} 1730, 1650
CH ₂ =CCH ₂ -N N-COC1 CH ₃	ii ·	ν _{C=0} 1730, 1650

Table 2 (Cont'd)

CH ₃ CH O CHCH ₂ -N N-COC1 (trans-)	Oily material	ν _{C=0} 1730, 1650
ON-CH2-NN-COCI	m.p. 150 ⁰ C (decomp.)	ν _{c=0} 1670, 1720
CH3CO-N N-COC1	Oily material	ν _{C=0} 1790, 1720 - 1670
0 -co-n n-coc1	· 11	ν _{C=O} 1790, 1710,
O CH3-N N-COC1 O	11	√ _{C=O} 1790, 1710 - 1660
O CH2-N N-COC1	tt .	√ _{C=0} 1790, 1710 - 1660
O O	m.p. 94 - 95°C (decomp.) (from CH ₂ Cl ₂ - Et ₂ O)	√ _{C=0} 1790, 1680
O O CH3COOCH2CH2-N N-COC1	Oily material	√ _{C=0} 1790, 1720, 1670

Table 2 (Cont'd)

O O CH3CH2-N N-COC1	m.p. 95 - 96 ⁰ C (decomp.) (from AcOBu)	ν _{C=0} 1780, 1660
CH3CH2CH2-N N-COC1	Oily material	ν _{C=0} 1780, 1710 - 1640
O O CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	11	ν _{C=0} 1780, 1660
O O (CH ₃) ₂ CH-N N-COC1	m.p. 130 - 131 ⁰ C (decomp.)	ν _{C=0} 1780, 1660
O O CH ₃ (CH ₂) ₃ CH ₂ −N N-COC1	Oily material	ν _{C=0 1790} , 1720 - 1665
CH ₃ (CH ₂) ₄ CH ₂ -NN-COCL	t†	V _{C=0} 1780, 1720 → 1640
ch ₃ (ch ₂) ₅ ch ₂ -N_N-cocl		ν _{C=0} 1780, 1720 - 1640
CH ₃ (CH ₂) ₆ CH ₂ -N N-COC1	t t	ν _{C=0} 1780, 1720 - 1640
O O V CH ₂ =CHCH ₂ -N N-COC1	Crystal	√ _{C=0} 1775, 1660 - 1620

Table 2 (Cont'd)

O O O	Crystal	ν _{C=0} 1785, 1720 - 1650
O O ClcH ₂ CH ₂ -N N-COCl	Oily material	√ _{C=0} 1790, 1720, 1680
O O CH3CH2-N N-COCL CH3	m.p. 65 - 70 ⁰ C (decomp.)	ν _{C=0} 1785, 1680
0 0 CH3CH2-N N-CSC1	m.p. 100 - 101°C	√ _{C=0} 1725, 1675
O H) HN N-COCI	m.p. 180 - 181°C	ν _{C=O} 1740, 1695
O H O-CH ₂ -N N-COC1	m.p. 160 - 165 ⁰ C	√ _{C=0} 1740, 1670
Cl3CCH2OCO-N N-COC1	Oily material	√ _{C=0} 1800, 1750,

25

5

10

15

20

25

acid

Table 2 (Cont'd)

O HN N-COCI	m.p. 185 - 187 ⁰ C (decomp.)	√ _{C=0} 1730, 1690
OOC1 HN_N-COC1 O	Oily material	√ _{C=0} 1750, 1710 - 1685
OCH ₂ -N N-COCL	11	V _{C=0} 1735, 1725, 1710, 1675

Note: $Et_2O = CH_3CH_2OCH_2CH_3$ $AcOBu = CH_3COO(CH_2)_3CH_3$

The compound represented by the general formula (V) can be easily obtained by reacting, for example, a salt with an alkali metal, an alkaline earth metal or a nitrogencontaining organic base of an amino acid (IX) (any of D-isomer, L-isomer and racemic compound) represented by the general formula (IX)

 H_2N —R—COOH (IX)

wherein R is as defined previously, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III) in a solvent inert to the reaction in the presence of an acid-binding agent. Preferable examples of the compound of formula (V) are D-isomers, L-isomers and racemic compounds of the following compounds, though it is needless to say that the examples are not limitative:

α - (4 - Acetyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Chloroacetyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Palmitoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Capryloyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Capryloyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Cyclohexanecarbonyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Benzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Benzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - P - Chlorobenzoyl - 2 - οxο - 1 - piperazinocarbonylamino) phenylacetic acid

	α - [4 - (3,4,5 - Trimethoxybenzoyl) - 2 - oxo - 1 - piperazinocarbonylamino]-		
	phenylacetic acid α - [4 - (2,4 - Dichlorobenzoyl) - 2 - οχο - 1 - piperazinocarbonylamino]phenyl-		•
5	acetic acid $\alpha - (4 - Acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic$	5	
	acid α - (4 - Methanesulfonyl - 2 - οχο - 1 - piperazinocarbonylamino)phenylacetic	=	*
	acid α - (4 - Acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic	10	
10	acid a - (4 - Phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-	10	
	acetic acid $\alpha - (4 - \text{Ethoxycarbonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid $\alpha - (4 - \text{Pivaloyloxymethyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic		
15	acid $\alpha - (4 - n - \text{Hexyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid	15	
	$\alpha = (4 - n - Butyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha = (4 - n - Butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-$		
20	acetic acid \[\alpha - (4 - n - Octyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid	20	
	α - (3 - Oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (2,5 - Dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid		
	$\alpha = (5 - \text{Methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid $\alpha = (2 - \text{Ethoxycarbonylmethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenyl-		
25	acetic acid	25	~
	α - (2 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic		
	acid α - (4 - Phenylaminocarbonyl - 3 - οχο - 1 - piperazinocarbonylamino)phenyl-		
30	acetic acid	30	
30	α - (4 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - n - Butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid		-
	$\alpha = (4 - \text{Ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid		
	vz - (4 - Isopropyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid	25	
35	α - (4 - n - Pentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - iso - Pentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid	35	•
	$\alpha = (4 - n - Hexyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid$		
	α - (4 - n - Heptyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - n - Octyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid		
40	w = (4 - n - Dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid	40	
70	α - (4 - Cyclopentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (2 - Methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-		
	acetic acid		
	α - (4 - n - Butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid	45	
45	$\alpha - (4 - n - Butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$		
	acetic acid $\alpha - (2 - Phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid$		
	α - (4 - Benzyl - 3 - 0x0 - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Carbamoyl - 2 - methyl - 3 - 0x0 - 1 - piperazinocarbonylamino)phenyl-	50	
50	acetic acid	30	Ð
	α - (4 - β - Hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid		ş-
	a - (4 - Allyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid		Q
55	$\alpha - (4 - \alpha - \text{Methylallyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid $\alpha - (4 - \beta - \text{Methylallyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid	55	_
	$\alpha = [4 - (Trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonylamino] phenyl-$		
	acetic acid $\alpha - (4 - Morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic$	-	
60	acid	60	
	α - (4 - Ethyl - 3 - 0x0 - 1 - piperazinocarbonylamino) propionic acid α - (4 - Acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid		
	α - (4 - Benzoyl - 2.5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid	٠.	
	α - (4 - Methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid	65	
65	α - (4 - Delizyl - 2) - thorn - 1 - piperazinocatoonyminino/pitenymeette were		

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α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
               α - (4 - Acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic
        acid
              α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
              α - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid
 5
              α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
              \alpha - (4 - Isopropyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - n - Pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - n - Hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - n - Hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid
                                                                                                                        10
              α - (4 - n - Heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
10
              \alpha - (4 - n - Octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - Allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - Phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid \alpha - (4 - Phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid
               \alpha - (4 - \beta - Chloroethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic
                                                                                                                        15
         acid
15
               \alpha - (4 - Pyrrolidinoethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic
         acid
               \alpha - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenyl-
         acetic acid
                                                                                                                         20
               \alpha - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenyl-
20
         acetic acid
               \alpha - (6 - Methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-
         acetic acid
               α - (4,6 - Dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
                                                                                                                         25
               \alpha - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino) phenylacetic acid
25
               α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-
               \alpha - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienyl-
         acetic acid
               a - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-
                                                                                                                         30
 30
         dienylacetic acid
               \alpha - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-
         dienylacetic acid
               \alpha - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic
                                                                                                                         35
 35
              \alpha - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid
              \alpha - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic
        acid
              α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic
                                                                                                                         40
 40
              \alpha - (2,2 - Pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-
        acetic acid
              \alpha - (4 - Benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-
        amino) phenylacetic acid
              \alpha - (4 - \beta, \beta, \beta - Trichloroethoxycarbonyl - 2,2 - pentamethylene - 3,5 - dioxo - 1-
                                                                                                                         45
 45
        piperazinocarbonylamino) phenylacetic acid
              \alpha - (3,5 - Dioxo - 1 - piperazinocarbonylamino) phenylacetic acid
              \alpha - (2 - Methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-
        acetic acid
                                                                                                                         50
              α - (4 - Benzyl - 2 - methyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-
 50
         acetic acid
              \alpha - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
              As the reactive derivative in the carboxyl group of the compound represented by
         the general formula (V), there is used a reactive derivative of a carboxylic acid which
         is ordinarily used in the synthesis of acid amides. Such reactive derivative includes, for
                                                                                                                         55
 55
         example, acid halides, acid anhydrides, mixed acid anhydrides with organic or inorganic
         acids, active acid amides, acid cyanides or active esters. Particularly, acid chlorides,
         mixed acid anhydrides and active acid amides are preferable. Examples of the mixed
         acid anhydrides are mixed acid anhydrides with substituted acetic acids, alkyl carbonic
         acids, aryl carbonic acids and aralkyl carbonic acids; examples of the active esters are
                                                                                                                         60
 60
         cyanomethyl esters, substituted phenyl esters, substituted benzyl esters or substituted thienyl esters; and examples of the active acid amides are N-acyl saccharins, N-acyl
                         N-acyl benzoylamides, N,N-dicyclohexyl-N-acylureas or N-acyl
         imidazoles,
         sulfonamides.
               Compounds of formula (VI) can be obtained by, for example, process (1) or (2).
                                                                                                                         65
 65
```

	Some of the compounds obtained by process (3) can further be used as the starting compounds in process (3). Any of D-, L- and racemic compounds of formula (VI)	
	may be used. The modes of practice of the processes (1), (2) and (3) are explained below.	š
5	The processes (1) and (2) may be carried out under substantially the same conditions. That is, the compound of formula (II) or (IV) is dissolved or suspended in at least one inert solvent selected from, for example, water, acetone, tetrahydrofuran,	J R
	dioxane, acetonitrile, dimethylformamide, methanol, etnanol, methoxyethanol, diethyl acetate	10
10	and methyl isobutyl ketone. The resulting solution or suspension is reacted with a reactive derivative of the compound of formula (III), or with the compound of formula (V) or a reactive derivative in the carboxyl group of the compound of formula (V) in	
4.	preferably from -40° to 30°C. The reaction time is ordinarily 5 minutes to 5 hours. Framples of the base used in the above reaction are inorganic bases such as alkali	15
15	hydroxides, alkali hydrogencarbonates, alkali carbonates, or alkali acetates; tertiary amines such as trimethylamine, triethylamine, tributylamine, pyridine, N-methylpiperidine, N-methylmorpholine, lutidine and collidine; and secondary amines such as didine, N-methylmorpholine, lutidine and collidine; and secondary amines such as di-	
20	cyclohexylamine or diethylamine. When the compound of formula (V) is used in the	20
20	effected in the presence of a dehydrating condensing agent such as N,N-dicyclohexyl carbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodiimide, N,N'-diethyl carbodiimide, N,N'-carbonyl (2-methylimidazole), a trialkyl ester of phosphorous acid, ethyl imide, N,N'-carbonyl (2-methylimidazole)	
25	ester of polyphosphoric acid, phosphorus oxychioride, phosphorus trichioride, 2-chioro-	25
23	includes alkali metal salts, alkaline earth metal salts, ammonium salts, and salts with organic bases such as trimethylamine or dicyclohexylamine. The process (3) is carried out in the manner described below.	
20	When B in the formula (VI) is a group other than a netero aromatic N-oxide this	30
30	(VII) or a tertiary amine in at least one solvent selected from, for example, water,	-
35	isobutyl ketone, tetrahydrofuran, dioxane, acetonitrile, ethyl acetate, methoxyethanol, dimethoxyethane, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform and a dichloroethane. The above-mentioned reaction is preferably effected in a	35
	strongly polar solvent such as water. In this case, the pH of the reaction solution is advantageously maintained at 2 to 10, preferably 4 to 8. The desired pH may be attained by addition of a buffer solution such as sodium phosphate. The reaction con-	-
40	ditions are not particularly limited, though the reaction is ordinarily conducted at 0 to	40
•	aromatic N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide group in the molecule, the compound of formula (VI) is reacted with the compound of formula (VII) in the above-mentioned solvent in the presence of a cupric	4.5
45	alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, benzyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, benzyl alcohol	45
	ceeds smoothly by using an excess of the alcohol per se to allow it to act as the reaction	50
50	ones, such as cupric chloride, bromide, fluoride, nitrate, surfate, borate, phosphate, cyanide, formate, acetate, propionate, citrate, tatarate, benzoate and salicylate. The amount of the cupric compound used is preferably 1/2 mole per mole of the compound	50
	of formula (VI). The reaction temperature and the reaction time may be varied dependence of formula (VI), cupric compound and compound of	55
55	formula (VII), though they are usually selected from the range of 0° to 100°C and the range of several minutes to several days, respectively. The reaction conditions to be adopted in the processes (1), (2) and (3) are not reaction conditions to be adopted in the processes (1), (2) and (3) are not reaction conditions.	JJ .
60	limited to those mentioned above, and can be properly varied depending upon the kinds of reaction reagents. Further, the non-toxic salts of the general formula (I), in which R ¹ is a salt-	60
60	forming cation, can be easily obtained according to an ordinary procedure from compounds of the general formula (I), in which R ¹ is a hydrogen atom or a blocking group. Thus among the compounds of formula (I) of the present invention, the penicillins	
	can be easily obtained according to any of the aforesaid processes (1) and (2), while	÷

21	1,500,002	- 31
	the cephalosporins can be easily obtained according to either the aforesaid process (1), (2) or (3).	· · · · · · · · · · · · · · · · · ·
5	The present penicillins and cephalosporins include concretely the following compounds though are not restricted thereto. The following penicillins can be produced by any of the aforesaid processes (1) and (2), and the following cephalosporins can be produced by any of the aforesaid processes (1), (2) and (3).	_ 5
•	Penicillins: 6 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-	
10	amido penicillanic acid,	10
10	 6 - [D(-) - α - (4 - dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido]penicillanic acid, 6 - [D(-) - α - (4 - enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl- 	10
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	
15	amino) phenylacetamido I penicillanic acid.	15
	$6 - [D(-) - \alpha - (4 - acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	•
	$6 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	
20	$6 - [D(-) - \alpha - (4 - n - hexyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetamido) penicillanic acid.$	20
	$6 - [D(-) - \alpha - (4 - n - butyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
7.00	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonyl-$	25
. 25	amino)phenylacetamido]penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-$	25
	acetamido] penicillanic acid, 6 - $[D(-)$ - α - $(4$ - pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)-	_
30	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - palmitoy)] - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	30
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{capryloyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{phenyl-}$	
	acetamido] penicillanic acid, 6 - [D() - α - (4 - caproyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-	
35	antomidal papicillagic acid	.35
	6 - $[D(-) - \alpha - (4 - \text{chloroacetyl} - 2 - 0x0 - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	•
40	$6 - [D(-) - \alpha - (4 - benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	40
40	$6 - [\widetilde{D}(-)] - \alpha - (4 - p - \text{chlorobenzoyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	40
	6 - $[D(-) - \alpha - (4 - p - methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
45	$6 - \{D(-) - \alpha - [4 - (3,4,5 - trimethoxybenzoyl) - 2 - oxo - 1 - piperazino-$	45
	carbonylamino] phenylacetamido} penicillanic acid, $6 - \{D(-) - \alpha - [4 - (2,4 - dichlorobenzoyl) - 2 - oxo - 1 - piperazinocarbonyl-$	
	amino] phenylacetamido) penicillanic acid, $6 - [D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	
50	amino)phenylacetamido]penicillanic acid, $6 - [D(-) - \alpha - (4 - phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	50
3	amino)phenylacétamido]penicillanic acid, 6 - $[D(-) - \alpha - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, 6 - [D(-) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacet-	
_ 55	amidol nenicillanic, acid.	55
	$6 - [D(-) - \alpha - (4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
60	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	60
	$6^{2} - [D(-) - \alpha - (4 - isopropyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetamidol penicillanic, acid$	00
	$6 - [D(-) - \alpha - (4 - n - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
	accounted benefitante acia?	

	$6 - [D(-) - \alpha - (4 - iso - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (2 - methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonyl-$	
5	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	5
	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	
	amino) phenylacetamido) penicillanic acid.	=
10	$6 - [D(-) - \varkappa - (4 - benzyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] penicillanic acid,$	10
	$6 - [D(-) - \alpha - (4 - \beta - hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido]penicillanic acid, 6 - [D(—) - α - (4 - acetyl - 2 - methyl - 3 - oxo - piperazinocarbonylamino)-	
15	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	15
	amino)phenylacetamido] penicillanic acid, 6 - [D(-) - α - (3 - οχο - 1 - piperazinocarbonylamino)phenylacetamido] peni-	
	cillanic acid.	
20	6 - [D(-) - vz - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,	20
	$6 - [\hat{\mathbf{D}}(-) - \alpha - (5 - \text{methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
	amido] penicilanic acid, $6 - [D(-) - \alpha - (2 - \text{ethoxycarbonylmethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonyl}$	
25	amino)phenylacetamido]penicillanic acid, 6 - $[D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	25
	amidol penicillanic acid.	
	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] penicillanic acid,	
30	$6 - [D(-) - \alpha - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido penicillanic acid,$	30
50	$6 - [D(-) - \alpha - (4 - \alpha - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)$	
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \beta - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
35	phenylacetamido] penicillanic acid, $6 - \{D(-) - \alpha - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonyl-$	35
3	aminol phenylacetamido) penicillanic acid.	
	6 - $[D(-) - \alpha - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
40	6 - $[\hat{D}(-) - \alpha - (4 - n - \text{heptyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido) penicillanic acid,	40
40	$6 - [D(-) - \alpha - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
45	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - cyclopentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	45
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonyl-$	
	amino) nhenylacetamido I nenicillanic acid.	
50	6 - [D(-) - α - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,	50
	$6 - [\overline{D}(-)] - \alpha - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	-
55	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	55
	acetamido]penicillanic acid, 6 - [D(-) - α - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-	2
	acetamido l penicillanic acid.	
60	6 - $[D(-) - \alpha - (4 - benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	60
	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	•
	$6 - [\hat{D}(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
	acetamido]penicillanic acid,	

	$6 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	
÷ _	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	5
5	phenylacetamidol penicillanic acid.	J
=	$6 - [D(-) - \alpha - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	
40	$6 - [D(-) - \alpha - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido penicillanic acid,$	10
10	$6 - [\hat{D}(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \beta - \text{chloroethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
15	phenylacetamidó] penicillanic acid, 6 - $[D(-)$ - α - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-	15
13	amino) phenylacetamido] penicillanic acid, 6 - [D(-) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -	
	phenylacetamidal nenicillanic acid.	
20	6 - $[D(-)$ - α - $(4 - n$ - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] penicillanic acid,	20
20	$6 - [D(-)] - \alpha - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	•
25	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	25
23	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinothiocarbonylamino})$	
	mbanylacetamidol nenicillanic acid	-
30	6 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] penicillanic acid,	30
	6 - [D(-) - a - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-	
	$6 - ID(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-$	
35	cyclohexadienylácetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - 1,4-$	35
	cyclohexadienylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	1,4 - cyclohexadienylacetamido [penicillanic acid, 6 - $[D(-)$ - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-	
40	cycloheyadienylacetamidol nenicillanic acid.	40
	$6 - [DL - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-thienylacetamido] penicillanic acid,$	
	$6 - [DL - \alpha - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetamido] penicillanic acid,$	
45	$6 - \widehat{DL} - \alpha - (4 - n - \text{propyl} - 2, 3 - \text{dioxo} - 1 - \text{piperadinocarbonylamino}) - 2$	45
	thienylacetamido] penicillanic acid, 6 - [DL - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-	
	thienylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-$	
50	amino) phenylacetamido l penicillanic acid,	50
± .	$6 - [D(-) - \alpha - (3.5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}]$ - penicillanic acid,	
	6 - [D(-) - α - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,	
<u>.</u> 55	$6 - [D(-) - \alpha - (4 - \text{benzyl} - 2, 2 - \text{pentamethylene} - 3, 5 - \text{dioxo} - 1 - \text{piperazino-carbonylamino})$ phenylacetamido] penicillanic acid,	55
	$6 - [D(-)] - \alpha - (4 - \beta, \beta, \beta - \text{trichloroethoxycarbonyl} - 2, 2 - \text{pentamethylene} - 3, 5 - 3, 5 - 3, 5 - 3, 6 - 3, $	
	dioxo - 1 - piperazinocarbonylamino) phenylacetamido] penicillanic acid, 6 - $[D(-)]$ - α - $(4$ - benzyl - 2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piper-	۲0
60	azinocarbonylamino) phenylacetamido] penicillanic acid, pivaloyloxymethyl 6 - $[D(-)$ - α - $(2$ - methyl - 3 - ∞ - 1 - piperazino-	60
	carbonylamino)phenylacetamido]penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	
	amino)phenylacetamido]penicillanate,	65
65		. 00.

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	phthalidyl 6 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido] penicillanate,	
	phthalidyl 6 - $[D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazino-carbonylamino) phenylacetamido] penicillanate,$	5 -
5	phthalidyl 6 - $[D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)$ phenylacetamido] penicillanate,	3
	methoxymethyl $6 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanate, methoxymethyl $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl-}]$	=
10	amino) phenylacetamido] penicillanate, methoxymethyl $6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazino-$	10
	carbonylamino)phenylacetamido]penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazino-$	
15	carbonylamino)phenylacetamido]penicillanate, methoxymethyl 6 - [D(—) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino- carbonylamino)phenylacetamido]penicillanate,	15
	pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate,$	
20	pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	20
20	pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - n - \text{octyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazino-carbonylamino})$ phenylacetamido]penicillanate,	
:	β - piperidinoethyl 6 - $[D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate, \beta - piperidinoethyl 6 - [D(-) - \alpha - (4 - n - octyl - 2, 3 - dioxo - 1 - piperazino-$	25
25	carbonylamino)phenylacetamido]penicillanate, $B - \text{morpholinoethyl } 6 - [D(-) - \alpha - (4 - \text{methyl } - 2,3 - \text{dioxo } - 1 - \text{piperazino} - 1,0)$	23
	carbonylamino) phenylacetamido] penicillanate and β - morpholinoethyl 6 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-	20
30	carbonylamino)phenylacetamido]penicillanate. Cephalosporins:	30
	$7 - \hat{I}D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamidol - 3 - methyl - \Delta^3 - cephem - 4 - carboxylic acid.$	
35 .	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - methyl - Δ^{0} - cephem - 4 - carboxylic acid,	35
	7 - $[D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - methyl - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	
40	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	40
	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	
45	phenylacetamido] - 3 - methyl - Δ^8 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	. 45
43	7 - $[D(-) - \alpha - (4 - n - \text{octyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	
	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	50 :
50	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	50
	acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)]$ - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	
55	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,	55=
	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino) - phenylacetamido] - 3 - acetoxymethyl - \Delta^3 - cephem - 4 - carboxylic acid,$	
60	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3 - cephem - 4-$. 60
	carboxylic acid, $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenyl-acetamido}] - 3 - [2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) \text{thiomethyl}] - \Delta^2 - cephem - 4-$	<i>.</i>
65	carboxylic acid,	65

		
,	7 - $[D(-)$ - α - $(4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3-cephem - 4 - carboxylic acid,$	-
5	7 - $[D(-)$ - α - $(4 - n$ - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - $[2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3 - cephem - 4-carbonylic acid$	5
ā .	7 - $[D(-) - \alpha - (4 - \text{phenyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamno})$ nenyl-acetamido] - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl})$ thiomethyl] - Δ^3 - cephem - 4-carbonylic acid	
10	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ nenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl})$ thiomethyl] - Δ^3 - cephem - 4-carboxylic scid.	10
15	$7 - [D(-) - \alpha - (4 - \text{ethyl} - 6 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl-amino})$ phenylacetamido] $-3 - [5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}]$	15
	7 - $[D(-) - \alpha - (4,6 - \text{dimethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl})\text{thiomethyl}] - \Delta^3- cephem - 4 - carboxylic acid.$	~
20	7 - $[D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	20
	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl)thiomethyl] - Δ^8 - cephem - 4 - carboxylic acid,	25
25	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	
30	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[2 - (1 - \text{methyl} - 1, 3, 4 - \text{triazolyl})$ thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	30
	$7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - [2 - (1 - \text{methyl} - 1,3,4 - \text{triazolyl}) \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	
35	$7 - [D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	35
40	$7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p-$	40
40	hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	
45	acetamido] $\stackrel{?}{-}$ 3 - azidomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	45
	7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	
50	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid.$	50
55	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid.$	55
<u>.</u>	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[5 - (1,2,3,4 - \text{tetrazolyl})$ thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid.	
60	7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	60
65	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - $[3$ - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl) thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-	65

36	1,500,002	
	acetamido] - 3 - [2 - (4 - methyloxazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	
	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino] phenylacetamido] - 3 - [2 - (4 - methylthiazolyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	· 5
5	acid, $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] - 3 - [2 - (pyridyl - 1 - oxide) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	
10	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - (2 - thiazolinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (1 - methylimidazolyl) thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	10
15	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - pyrimidinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (6 - methylpyridazinyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	15
20	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [1 - (4 - methylpiperazino)thiocarbonylthiomethyl] - \Delta^3 - cephem-4 - carboxylic acid,$	20
	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5$ - (3 - methylisoxazolyl)carbonylthiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	•
25	7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	25
30	7 - [D(-) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-	30
35	carboxylic acid, $7 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid.$	35
	7 - $[D(-)$ - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ° - cephem-4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-	40
40	amido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid.	40
45	7 - $[D(-)$ - α - $(4$ - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4$ - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-	45
50	4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet- amido] - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	50
	7 - $[D(-)$ - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl})$ - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	~
55	7 - $[D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem-4 - carboxylic acid.$. 55
60	7 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - [D(-) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-	60
	phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 -cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-	

	amido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid.	
_	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
5	amido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	5
3		3
3	7 - $[D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] -$	•
	Δ ³ - cephem - 4 - carboxylic acid,	
	$7 - [D(-) - \alpha - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	
10	amido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-	10
	carboxylic acid,	
	$7 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet	
	amido] - 3 - $[5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-$	
	carboxylic acid,	
15	$7 - [D(-) - \alpha - (3.5 - \text{diox} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}]$	15
	$3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^8 - cephem - 4 - carboxylic$	
	acid,	
	7 - $[D(-)$ - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-	
	acetamido] - 3 - [D - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-	
20	4 - carboxylic acid, and	20
	methoxymethyl 7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	
	carbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.	
	The susceptible test of typical compounds among the compounds of the present	
	invention are shown below.	
25	(1) The minimum inhibitory concentrations (MIC) of the compounds against	25
	different standard strains are shown in Tables 3 and 4.	
	The minimum inhibitory concentration (MIC) was determined by the plate method	
	disclosed in "Chemotherapy" (Japan), Vol. 16, (1968), pages 98-99. The culture	•
	medium used was a Heart infusion agar (pH 7.4). The number of the cells per plate	
30	used in the inoculum was 10 ⁴ (10 ⁶ cells/ml).	30

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Proteus vulgaris 3027	> 200	< 1.57	0.79	3.13
Klebsiella pnewnoniae	50	> 200	> 200	12.5
Pseudomonas aeruginosa I.F.O.	> 200	50	. 20	. 25
Escherichia coil NIHJ	< 1.57	< 1.57	1.57	< 1.57
Staphylo- coccus aureus 209p	< 1.57	< 1.57	5.15	< 1.57
Compound	CO-CHCONH CS CH3 (Sodium Ampicilin) NH2 0 COONA	COONA COONA COONA COONA	CO-CHCONH SCH3 (Sodium Sulbenicillin) So ₃ Na O CCONa	Hycon NCONHCHCONH T S CH3 COONB
Com- pound No.		(Control)		н

Table 3 (Cont'd)

~	C12CHCON NCONHCHCONH S CH3	< 1.57	< 1.57	50	12.5	6.25
3	(H)-con Nconhchconh S CH ₃	< 1.57	< 1.57	001	3.13	3.13
4	CH ₃ CON NCONHCHCONH S CH ₃ CH ₃ CON NCONHCHCONH CH ₃ O N COONA	< 1.57	< 1.57	25	12.5	3.13
ſΛ	CH ₃ SO ₂ N NCONHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CON ₈	< 1.57	< 1.57	25	12.5	< 1.57

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Table 3 (Cont'd)

و	CH ₃ (CH ₂) ₃ CH ₂ CON NCONHCHCONH CH ₂ CH ₃ CH ₃ CH ₃ CH ₃ COON _a	3.13	5.13	95	6.25	6.25
٢	O-con nconherconh secons	< 1.57	< 1.57	200	12.5	6.25
8	C1-(C)-CON NCONH CHCONH S CH3	< 1.57	1.57	00τ	6.25	3.13
6	CH3-CO-CON NCONHCHCONH SXCH3	< 1.57	3.13	001	3.13	3.13

Table 3 (Cont'd)

10	C1 C)-CON NCONHCHCONH S CH3 CH2 CH2 COONB	< 1.57	> 1.57	100	6.25	3.13
ננ	CH ₂ CONHCON NCONHCHCONH CH ₂ S CH ₂ CH ₂ CH ₂ CH ₂ CH ₃ CONHCON CONH CH ₂ CON CH ₃ CON ₁ CH ₂ COON CH ₃ CON CH ₃	< 1.57	< 1.57	20	05 .	6.25
12	CH ₂ CH ₂ CCON NCONHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃	< 1.57	3.13	. 50	6.25	12.5
13	CH ₂ (CH ₂) ₄ CH ₂ N NCONHCHCONH SCH ₂ O COONa	< 1.57	< 1.57	25	< 1.57 < 1.57	< 1.57

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Table 3 (Cont'd)

14 GH ₃ (CH ₂) ₂ CH ₂ N CONHCHOONH S CH ₃ CH ₂ CH ₂ CH ₂ N CONHCHOONH S CH ₃ N CONHCHOONH S COONA CH ₃ CH ₃ N CONHCHOONH S COONA CH ₃ N CONHCHOONH S CH ₃ N CONHCHOONH S CH ₃ N CONHCHOONH S COONA CH ₃ N CONHCHOONH S CH ₃ N C C CH ₃ N C CH ₃ N C CH ₃ N C C C C C C C C C C C C C C C C C C C							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	14	CH ₂ (CH ₂) ₂ CH ₂ N NCONHCHCONH	< 1.57	< 1.57	25	3.13	< 1.57
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	15	CH ₃ (CH ₂) ₂ CH ₂ N NCONHCHCONH SCH ₃ CH ₃	75.1 >	5.13	50	6.25	6.25
СН3N NCONHCHCONH	16	CH ₂ (CH ₂) ₆ CH ₂ N NCONHCHCONH S CH ₃ O COONa	< 1.57	< 1.57	12.5	1.57	< 1.57
	_	CH ₂ N NCONHCHCONH T S CH ₂ CH ₂ CH ₂ CH ₃ C	< 1.57	, 5 1.57	12.5	50	6.25

Table 3 (Cont'd)

Β	CH ₂ (CH ₂) ₂ CH ₂ N NCONHCHCONH	< 1.57	< 1.57	12.5	25	3.13
19	CH ₃ CH ₂ N CONHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ COONa	< 1.57	< 1.57	12.5	50	5.13
50	(CH ₃) ₂ CHN NCONHCHCONH SCH ₃ O COONB	3.13	< 1.57	12.5	25	3.13
21	(CH ₃) ₂ CHCH ₂ CH ₂ N NCONHCHCONH	62.0>	1.57	. 55	. 25	3.13

Table 3 (Cont'd)

22	CH ₂ (CH ₂) ₂ CH ₂ ONHCHCHCONH	< 1.57	< 1.57	20	12.5	6.25
23	O CH2N NCONHCHCONH SCH3	< 1.57	< 1.57	25	6.25	3.13
. 24	HOCH2CH2N NCONHCHCONH SCH3	3.13	< 1.57	90	50	25
25	CH2=CHCH2N NCONHCHCONH SCH3	< 1.57	< 1.57	25	50	3.13

Table 3 (Cont'd)

26	CH2=CHCHN NCONHCHCONH SCH2	< 1.57	< 1.57	23	25	12.5
27	CH ₂ =ccH ₂ N NCONHCHCONH SCH ₃ CH ₃ CH ₃ CH ₃ CH ₃	< 1.57	< 1.57	25	25	3.13
28	CH ₃ CH O CHCH ₂ N NCONHCHCONH S CH ₃ CH ₃ (trans-)	< 1.57	< 1.57	25	. 25	3.13
29	$c_{H_3(c_{H_2})_4}^{\circ}c_{H_2}^{\circ}$ Coons $c_{N_3}^{\circ}c_{H_3}^{\circ}c_{N_3}^{\circ}$	3.13	< 1.57	12.5	3.13	3.13

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30	CH ₃ (CH ₂) ₆ CH ₂ NCONHCHCONH	< 1.57	< 1.57	25	6.25	3.13
31	CH ₂ (CH ₂) ₁₀ CH ₂ NCONHCHCONH	< 1.57	< 1.57	12.5	6.25	< 1.57
32	H-N NCONHCHCONH SCH3 CH3	/51.57	< 1.57	12.5	12.5	6.25
33	O-nhcon nconhchconh Sch3	< 1.57	< 1.57	50	6.25	3.13

Table 3 (Cont'd)

34	O-con n conechconh s ch3	1.57	3.13	100	50	50
35	O-ch2N NCONECHCONH SKCH3	1.57	6.25	100	52	25
36	CH ₃ CH ₂ N NCONHCHCONH SCH ₃	< 1.57	< 1.57	6.25	< 1.57	< 1.57
37	CH3/N CONHCHCONH SCH3	< 1.57	< 1.57	6.25	6.25	< 1.57

Table 3 (Cont'd)

38	CH2CH2CH2N NCONHCHCONH — S CH3	0.4	< 0.1	6.25	3.13	4.0
	o √ N → cooka					
39	CH ₂ (CH ₂) ₂ CH ₂ NCONHQHCONH CH ₃ CH ₂ CH ₃ CH	0.4	< 0.1	6.25	1.57	0.4
40	(CH ₃) ₂ CHN NCONHCHCONH (SYCH ₃) (O)	0.4	< 0.1	6.25	3.13	4.0
41	CH3COOCH2CH2N NCONHCHCONH SKCH3	< 1.57	> 1.57	25	6.25	< 1.57

42	CH2=CHCH2N NCONHCHCONH T S CH3	1.57	< 1.57	12.5	6.25	< 1.57
43	O-N NCONHCHCONH T S CH3 CH3 COONB	< 1.57	< 1.57	6.25	1.57	< 1.57
44	C1CH2CH2N NCONHCHCONH S CH3	< 1.57	< 1.57	6.25	< 1.57	< 1.57
45	$c_{H_3}(c_{H_2})_3 c_{H_2} $ $c_{N_3}(c_{N_2})_3 c_{N_2}$ c_{N_3} c_{N_3} c_{N_3}	0.79	< 0.1	12.5	0.79	0.4

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Table 3

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46	CH ₂ (CH ₂) ₄ CH ₂ N NCONHCHCONH T S CH ₃	0.2	< 0.1	6.25	4.	0.4
47	CH ₂ (CH ₂) ₆ CH ₂ N NCONHCHCONH SCH ₃ (O) 0 COONB	. 2.57	< 1.57	6.25	<1.57	< 1.57
48	CH3N NCONHÇHCONH S CH3	< 0.4	< 0.4	6.25		۸ 4
49	CH ² NCONHCHCONH SCH ² OH CH ² OCO CH ² OC	< 0.4	0.79	12.5	12.5	1.57

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50	CH3N NCONHQHCONH SCH3	< 0.79	62.0 >	6.25	6.25	< 0.79
51	CH ₂ (CH ₂) ₆ CH ₂ N NCONHCHCONH S CH ₃ O COOCH ₂ OCH ₃	< 0.4	< 0.4	12.5	× 0.4	< 0.4
52	CH ₃ N NCONHCHCONH S CH ₃ CH	0.79	0.79	25	25	1.57
53	CH ₂ N NCONHCHCONH T S CH ₂ C	0.79	< 0.4	6.25	25	0.79

Table 3 (Cont'd)

,		•	
0.79	0.79	0.79	3.13
0.79	25	1.57	12.5
12.5	6.25	12.5	12.5
4.0	4.0	, 4.0	67.0 >
0.79	0.79	, o >	62.0 >
CH ₂ (CH ₂) 6 CH ₂ N NCONHCHCONH SCH ₃ CH ₃	CH ₃ N NCONHCHCONH S CH ₃ CH ₃ CH ₃ COCH ₂ CH ₂ N CO	CH ₂ (CH ₂) 6 CH ₂ N NCONHCHCONH T SYCH ₃ O	CH ₂ N NCONHCHCONH SCH ₃ CH ₃ COON _a
54	55	56	57

Table 3 (Cont'd)

58	CH ₂ N NCONHCHCONH S CH ₂ S CH ₃ CH ₂	< 1.57	. > 1.57	12.5	25	3.13	
59	HN NCONHQHCONH SCH3	< 1.57	< 1.57	25	500	3.13	

(Note) Sodium Carbenicillin and Sodium Sulbenicillin are regarded as preferable drugs at the level of this technical field, and hence are described for reference.

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Proteus vulgaris 3027	< 1.57	< 1.57	1.57	3.13
Klebsiella pneumoniae	100	001	200	200
Pseudomonas aeruginosa I.F.O.	> 200	> 200	> 200	200
Escherichia coli NIHJ	< 1.57	< 1.57	< 1.57	> 3.13
Staphylo- coccus aureus 209p	< 1.57	< 1.57	< 1.57	< 1.57
Compound	H2NCHCONH CH2OCOCH3 (Sodium Cephaloglycin)	S CH2CONH S CH2OCOCH3 (Sodium Cophalothin)	N=N N-CH2CONH	S-CH2CONH S CH2NO (Cephaloridine) < 1.57
Com- pound No.		(10	ortno5)	

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09	CH3N NCONHCHCONH S CH20COCH3	0.79	< 0.1	25	3.13	3.13
61	CH ₃ CH ₂ N NCONHCHCONH S CH ₂ OCOCH ₃	. > 0.79	< 0.79	. 52	3.13	3.13
62	CH ₃ N NCONHCHCONH S N-N CH ₂ S S CH ₃	0.79	بن٥ >	50	1.57	3.13
63	CH3N MCONHCHCONH S N-N CH2S N-N CH2S N-N CH3	< 0.79	< 0.79	25	< 0.79	1.57

64	CH3N NCONHCHCONH T S CH2S S	0.79	< 0.1	25.	1.57	5.13
65	CH ₃ N NCONHCHCONH S CH ₂ S N N N CH ₂ S N N N CH ₂ S N N CH ₃ N CH ₃	5.13	0.79	. 25	3.13	3.13
99	CH ₃ CH ₂ N NCONHCHCONH S N-N CH ₂ S N-N CH ₃	< 0.79	< 0.79	52	0.79	< 1.57

Table 4 (Cont'd)

67	CH3CH2N NCSNHCHCONH S CH2CCCCH3	6.25	< 0.79	100	3.13	12.5
89	CH ₃ N NCONHCHCONH S CH ₂ N CH	75*T	62.0 >	12.5	< 0.79	1.57
69	CH ₂ CH ₂ N NCONHCHCONH S CH ₂ S N N N CH ₂ CH ₂ S N N N CH ₃ CH ₂ S N N N N N N N N N N N N N N N N N N N	< 0.79	< 0.79	12.5	> 0.4	< 0.79

Table 4 (Cont'd)

0.7	CH ₂ CH ₂ N NCONHÇHCONH S CH ₂ S (Q)	< 0.79	1.57	100	1.56	1.56 < 0.79
17	CH ₃ N NCONHCHCONH S CH ₂ S N T CH ₃	60.79	< 0.79	50	1.56	< 0.79

as preferable drugs at the level of this technical field, and hence are Sodium Cephalothin, Sodium Cephazolin and Cephaloridine are regarded set forth for reference. (Note)

(2) The minimum inhibitory concentrations (MIC) of the compounds against clinical isolates of bacteria are shown in Tables 5 and 6.

MIC was determined in the same manner as in the preceding paragraph (1).

Table 5-1

Sodium		.1 P-2 P-3 P-4 P.	0.79	6.25 3.13 3.13 12.5 >200	6.25 3.13 6.25 6.25 > 200	5 3.13 6.25 >200	5 1.57 6.25 200	5 1.57 6.25 200	6.25 0.79 6.25 .100	3.13 0.79 0.79 3.13 100
Sodium	sneam s	998 SW 9	+	-		-	ļ		<u> </u>	_
Sodium	Stanhylococus		 	ļ	 	3.13	3.13	3.13	3.13	1.57
Sodium		MS MS	3.13	6.25	3.13	3.13	3.13	3.13	3.13	1.57
Sodium Ampicillin Sodium Carbenicillin Sodium Sulbenicillin Sulbenicillin " 13 " 14 " 16 " 30 "		-	6.25	6.25	3.13	6.25	3.13	3.13	3.13	1.57
Compound Sodium Ampicillin Sodium Carbenicill Sodium Sulbenicill " 1		MS 8619	< 0.4	0.79	3.13	1.57	0.79	0.79	< 0.4	< 0.4
Control		Compound	ß	Sodium Carbenicill	Sodium Sulbenicill	Compound No. 1	" 13	" 14	16	

Table 5-1 (Cont'd)

						·	
> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
6.25	6.25	6.25	6.25	6.25	6.25	6.25	12.5
1.57	3.13	0.79	1.57	0.79	1.57	62.0	1.57
3.13	1.57	1.57	1.57	3.13	1.57	1.57	1.57
12.5	12.5	6.25	6.25	6.25	6.25	6.25	6.25
3.13	3.13	3.13	3.13	3.13	3.13	1.57	3.13
3.13	3.13	3.13	1.57	3.13	3.13	3.13	3.13
6.25	12.5	6.25	3.13	12.5	6.25	6.25	6.25
3.13	5:13	3.13	1.57	3.13	3.13	1.57	3.13
0.79	67.0	0.79	0.79	0.79	0.79	<.0.4	< 0.4
. 36	37	38	39	6	45	46	47
Compound No. 36	2	=	=	=	.=	:	=

Table 5-2

L_{-}	· /				Escherichia coli					
٥	Compound	GN 3481	GN 3435	GN 3452	GN 3465	CN 3611	K-1	K-2	K-3	K-4
ОТ	Sodium Ampicillin	6.25	3.13	6.25		> 200	6.25	6.25	> 200	12.5
Contr	Sodium Carbenicillin	6.25	6.25	12.5	> 200	> 200	6.25	6.25	> 200	12.5
	Sodium Sulbenicillin	12.5	6.25	12.5	> 200	> 200	6.25	12.5	>200	6.25
٥	Compound No. 1	12.5	6.25	12.5	200		6.25	25 .	> 200	12.5
	" 13	6.25	3.13	3.13	25		3.13	6.25	100	6.25
	" 14	6.25	6.25	6.25	50		3.13	12.5	200	6.25
	. 16	3.13	1.57	1.57	12.5		1.57	3.13	50	3.13
	" 30	25	12.5	25	50	> 200	12.5	25	>200	12.5

Table 5-2 (Cont'd)

1.57	3.13	0.79	0.79	0.79	0.79	< 0.4	0.79
>200	> 200	>200	>200	>200	200	50	100
3.13 >200	6.25 >200	3.13 >200	1.57 >200	3.13 >200	1.57	0.79	1.57
3.13	12.5	3.13	1.57	1.57	62.0	0.79	1.57
> 200	> 200	> 200-	> 200	> 200	> 200	> 200	> 200
100	200	20	25	50	25	6.25	6.25
3.13	12.5	3.13	0.79	1.57	1.57	0.79	1.57
1.57	3.13	0.79	62.0	0.79	0.79	< 0.4	67.0
3.13	6.25	3.13	1.57	1.57	1.57	3.13	1.57
. 36	37	38	39	40	45	. 46	47
Compound No. 36		Ξ	=	-	11	=	z

Table 5-3

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	GN 383	> 200	50	50	50	20	50	25	12.5	50
	GN 244	> 200	50	50	52	50	50	12.5	25	50
	GN 163	> 200	50	50	25	25	25	12.5	12.5	25
	GN 2987	> 200	50	25.	. 52	12.5	12.5	3.13	12.5	12.5
nosa	GN 2565	> 200	200	100	50.	50	50	12.5	50	50
Pseudomonas aeruginosa	GN 1091	> 200	100	50	25	25	25	12.5	12.5	25
Pseu	GN 221	V 200	25	25	25	50	25	25	12.5	50
	GN 82	> 200	100	50	25	50	25	6.25	12.5	25
	918 ND	> 200	50	50	25	50	50	. 25	12.5	50
	GN 1035	> 200	> 200	100	100	50	50	25	100	50 .
	/	llin	odium Carbenicillin	Sulbenicillin	No. 1	13	14	16	19	30
	Compound	Sodium Ampicillin	02	-01	Compound No.	=	=	=	=	=
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Nable 5-3 (Cont'd)

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6.25	25	6.25	6.25	6.25	25	25	50
12.5	50	6.25	6.25	6.25	. 52	12.5	25
6.25	12.5	3.13	3.13	6.25	12.5	6.25	12.5
12.5	25	6.25	3.13	٤τ٠٤ ′	12.5	6.25	12.5
25	25	12.5	12.5	12.5	. 25	12.5	25
6.25	12.5	3.13	3.13	6.25	12.5	12.5	12.5
3.13	6.25	6.25	3.13	6.25	3.13	12.5	25
6.25	6.25	3.13	3.13	6.25	12.5	6.25	12.5
6.25	12.5	3.13	6.25	3.13	25	25	50
25	50	12.5	12.5	25	50 ,	50	25
0.36	37	38	39	40	45	46	47
Compound No. 36	=	=	=	=	=	=	=

Table 5-4

L_{-}		d	Pseudomonas aernginosa	aernginosa			Klehsiella pneumoniae	eumoniae	
٥	Compound	τ-s	S-2	£-8	8-4	GN 4117	GN 4081	GN 3850	GN 917
7	Sodium Ampicillin	> 200	> 200	> 200	> 200	> 200	> 200	50	25
Coatac	Sodium Carbenicillin	200	200	200	200	> 200	> 200		> 200
วอ	Sodium Sulbenicillin	00τ	700	001	00Ҭ	> 200	> 200	> 200	> 200
0	Compound No. 1	95	00τ	05	05	500	> 200	25	25
	" "	05	05	100	95	52	25	6.25	12.5
	" 14	05 .	95	. 001	50	. 50	50	12.5	25
	9T: "	12.5	52	05	25	25	25	3.13	12.5
	61 . "	95	20	05	05	> 200	> 200	100	50
	" 30	50	20	00τ	50	001	100	25	25

Table 5-4 (Cont'd)

<u>. </u>		· · · · ·		,			
6.25	12.5	3.13	1.57	6.25	1.57	0.79	1.57
12.5	25	6.25	3.13	12.5	3.13	1.57	3.13
001	200	50	25	100	25	12.5	12.5
100	100	50	25	50	25	12.5	12.5
50	100	12.5	12.5	12.5	25	50	50
25	50	12.5	25	25	50	50	50
12.5	25	12.5	12.5	52	25	95	50
50	500	12.5	12.5	12.5	.25	50	50
No. 36	37	38	39.	40	45	. 46	47
Compound No.	E	=	=	E	=	£	=

Table 5-

ı									
	/	Shigell	Shigella sonnel	Shigell	Shigella flexneri	Saimonella typhi	a typhi	Salmonella typhi-murium	ella rium
ğ	Compound	JS 11755	JS 11232	JS 11215	JS 11839	SL 2169	SI 819	SL 2136	SL 858
ğξ	Sodium Ampicillin	6.25	> 200		1.57	0.78	1.56	> 200	3.13
β.ά.	Sodium Carbenicillin	12.5	> 200	> 200	12.5	3.13	6.25	> 200	12.5
מאַ	Sodium Sulbenicillin	> 200	> 200	> 200	12.5	1.57	6.25	> 200	25
8.	Compound No. 1	12.5	> 200	100	£1.5	6.25	6.25	> 200	12.5
=	1.3	3.13	12.5.	12.5	1.57	3.13	6.25	200	0.79
=]	14	6.25	52	25	3.13	3.13	6.25	. 200	1.57
=	16	1.57	6.25	6.25	64.0	1,57	3.13	100	1.57
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cont.d -

Table 5-5 (Cont'd)

			,		<u>,</u>	,	
6.25	12.5	3.13	0.79	6.25	0.79	< 0.4	< 0.4
> 200	> 200	200	100	> 200	200	50	50
1.57	6.25	1.57	0.79	1.57	1.57	1.57	3.13
1.57	3.13	0.79	62.0	1.57	0.79	0.79	1.57
3.13	6.25	1.57	0.79	3.13	1.57	0.79	1.57
100.	> 200	25	25	. 50	. 25	6.25	6.25
50	100	50	25	. 05	25	12.5	6.25
3.13	6.25	3.13	1.57	3.13	1.57	0.79	62.0 .
No. 36	37	38	39	40	45	46	47
Compound No.	ŧ	=	= .	2	=	Ξ	E.

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Table 5-6

			Proteus		
Compound	punc	mirabilis	morganli	vulgaris	retigeri
Sod	Sodium Ampicillin	<i>ν</i> 1.57	< 1.57	< 1.5	200
Sod	Sodium Carbenicillin	0.8	0.4	0.8	> 200
Soci	Sodium Sulbenicillin	61.0	< 0.4	< 0.4	> 200
odmo	Compound No. 16	1.56	95*τ	8.0	6.25
-	30	3.13	3.13	3.13	12.5
_	36	6.0	<0.4	< 0.4	12.5
	37	61.0	0.79	4.0,>	25

Table 5-6 (Cont'd)

			· .		
12.5	6.25	6.25	6.25	3.13	0.79
< 0.4	< 0.4	< 0.4	< o.4	< 0.4	< 0.4
< 0.4	< 0.4	62.0	0.79	< 0.4	< 0.4
< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4
No. 38	39	40	45	46	47
Compound No. 38	=	z.	= .	=	=

Table 6-1

<u>/</u>	-				Staphylococcus aureus	aureus					
ပ	Compound	WS 8619	MS 8588	KI 8713	MS 8596	MS 8684	F-1	F-2	F-3	F-4	F-5
	Sodium Cephaloglycin	1.56	3.13	3.13	1.56	95°τ	3.13	1.56	1.56	3.13	25
гьот	Sodium Cephalothin	< 0.4	< 0.4	4.0>	< 0.4	< 0.4	<0.4 <0.4	<0.4	<0.4	< 0.4	1.56
.uoე	Sodium Cephazolin	4.0 >	< 0.4	< 0.4	< 0.4	4.0 >	0.78	0.78 < 0.4	<0.4	<0.4	0.78
]	Cephalorizine	,< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4 < 0.4	<0.4	<0.4	< 0.4	0.78
5	Compound No. 60	0.78	1.56	81.0	0.78	1.56	3.13	0.78	1.56	1.56	.50
	61	1.56	1.56	1.56	1,56	1.56	3.13	1.56	1.56	3.13	50
]	" 62	0.78	1.56	1.56	0.78	1.56	3.13	0.78	1.56	1.56	12.5

Table 6-1 (Cont'd)

7 5	1.56 3.13 0.78 1.56 1.56 1.56		1.56	1.56 1.56	3.13 1.56 1.56
	1.5		1.56	3.13 1.56	1.56 3.13 1.56
				_	
1.56 3.13 1.56 0.78		1.56	1.56 1.56	-	1.56

rable 6-

\angle					Escherichia coli	li.				
ບັ	Compound	GN 3481	GN 3435	GN 3452	GN 3465	GN 3611	K-1	K-2	K-3	K-4
	Sodium Cephaloglycin	. 51.5	95°τ	3.13	12.5	25	1.56	1.56	25	12.5
rtrol	Sodium Cephalothin	12.5	6.25	12.5	52	50	6.25	6.25	100	25
roʻʻ	Sodium Cephazolin	1.56	1.56	1.56	6.25	25	1.56	1.56	> 200	3.13
	Cephalorizine	3.13	3.13	3.13	. 05	00τ	3.13	3.13	200	6.25
<u> </u>	Compound No. 60	6.25	6.25	12.5	100	> 200	6.25	12.5	200	25
·	61	3.13	3.13	6.25	50	200	3.13	6.25	100	6.25
	62	6.25	6.25	6.25	25	200	6.25	12.5	200	12.5
	63	51.5	3.13	12.5	25	00τ	3.13	6.25	50	6.25

Cable 6-3

/			-	-	Pseu	Pseudomonas aeruginosa	jeso.	-	-		
٦	Compound	GN 1035	GN 376	GN 82	GN 221	1601 ND	GN 2565	GN 2987	GN 163	GN 244	GN 383
	Sodium Cephaloglycin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
roj	Sodium Cephalothin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
ταου	Sodium • Cephazolin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
	Cephalorizine	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
)	Compound No. 60	200	90	50	12.5	. 05	00τ	. 50	20	50	50
	π9 "	100	12:5	25	6.25	25	95	. 25	52	25	12.5
	62	200	001	100	50	00 T	00τ	50	20	100	100

cont'd

Table 6-3 (Cont'd)

25	12,5	52
50	25	25
25	12.5	12.5
25	12.5	12.5
50	50	50
50	12.5	12.5
25	3.13	6.25
50	6.25	12.5
50	12.5	12.5
100	90	50
¥0. 63	68	69
Compound No. 63	÷	£

Klebsiella pneumoniae	S-4 GN 4117 GN 4081 GN 917	>200 3.13 3.13 1.56	> 200 6.25 12.5 3.13	>200 3.13 3.13 1.56	> 200 12.5 12.5 3.13	100 25 25 6.25	50 12.5 12.5 6.25	200 25 12.5 6.25
aeruginosa	8-3	> 200	> 200	> 200	> 200	100	50	200
Preudomonas aeruginosa	8-2	> 200	> 200	> 200	> 200	700	50	500
	S-1	> 200	> 200	> 200	> 200	500	50	200
/	Compound	Sodium Cephaloglycin	Sodium Cephelothin	Sodium Cephezolin	Cephalorizine	Compound No. 60	61	. 62
	ວົ		trol	uoŋ		<u>ن</u>	<u> </u>	<u></u>

Table 6-4 (Cont'd)

	<u></u>	
3.13	1.56	0.78
6.25	-	ı
6.25	ı	•
100	25	50
700	25	50
100	25	25
100	52	52
No. 63	89	69
Compound No. 63	£	z

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×17.

Table 6-5

		Proteus	-	
Compound	mirabilis	morganil	vulgaris	rettgeri
Sodium Cephaloglycin	3.13	1.56	. 50	50
Compound No. 60	3.13	3.13	1.56	6.25
. 61	1.56	1.56	8.0	3.13
62	6.25	3.13	3,13	6.25
. 69	3.13	3.13	1.56	3.13
				-

(3) Resistant activity against β -lactamase, *Pseudomonas aeruginosa* GN 238: The resistant activity of each compound against β -lactamase was measured in the manner described below.

 β -Lactamase was prepared from Psuedomonas aeruginosa GN 238. This microorganism was cultured in 100 ml of a medium containing 2 g of yeast extract. 10 g of polypeptone, 2 g of glucose, 7 g of disodium hydrogen phosphate, 2 g of potassium dihydrogen phosphate, 1.2 g of ammonium sulfate and 0.4 g of magnesium sulfate, per liter, in a 500-ml Erlenmeyer flask for 6 hrs. at 37°C with shaking. The resulting cells were collected by centrifugation (5,000 r.p.m. × 10 min.), washed three times with 0.1 M phosphate buffer (pH 7.0). Subsequently, the cells were subjected to sonication (20 KH₂, 20 min.) and then centrifuged at 15,000 r.p.m. for 60 min. By using the supernatant of enzyme fluid, the resistance of each compound against β -lactamase was determined by the iodometric assay method. The results obtained were as set forth in Table 7. Each numeral shown in Table 7 is a relative activity value calculated by assuming as 100 the activity of the control Potassium Penicillin G.

Table 7

Comparison of resistant activity against β -lactamase

	Compound	Relative activity (%)
	Potassium Penicillin G	100
덩	Sodium Ampicillin	115
Control	Sodium Carbenicillin	116
ၓ	Sodium Sulbenicillin	50
d	compound No. 30	3
	" 36	14
	" 37	15
	" 38	15
	" 39	15
	n 40	15
	" 45	16
	" 46	12
	" 47	1

From Tables 3 to 6, it is understood that the compounds of the present invention have a broader antibacterial spectrum and more excellent antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species but also many drug-resistant bacteria than the control ampicillin and cephaloglycin, i.e. compounds having an amino group at the α -position of the acyl group. It is also understood from Table 7 that the compounds of the present invention are far higher in resistance to β -lactamase than the control drugs.

80	1,500,002	
	As is clear from the above results, the compounds represented by the formula	
	(Ie), among the compounds of the present invention, show prominent effects, and par-	
	ticularly preferable compounds are those of the formula (Ie), in which A represents a	
_	hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group;	5
5	and R ² and R ³ represent individually a hydrogen atom or an alkyl group.	3
	The present penicillins and cephalosporins have generally low toxicity. For	•
	example, $6 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido]penicillanic acid and $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 -$	-
	piperazinocarbonylamino) phenylacetamido] penicillanic acid have LD_{s_0} (i.v. in mouse	
10	having a weight of 19 ± 1 g) greater than 5 g/kg.	10
10	The compounds of formula (I) of the present invention may be administered not	
	only in the form of free acids but also in the form of non-toxic salts or physiologically	
	acceptable esters. Further, the compounds, which are in the form of physiologically	
	unacceptable esters, are ordinarily put into uses after bringing them to the form of free	
15	acids or non-toxic salts by removing the ester-forming group according to a conven-	15
13	tional procedure known in this technical field.	
-	The compounds of the present invention can be administered to humans and	
	animals after formulating them into a physiological form such as tablet, capsule, syrup,	
	injection or the like which is usually adopted in the case of penicillin and cephalosporin	
20	type drugs.	20
_,	Procedures for producing the compounds of the present invention are shown below	
	with reference to examples.	
	Example 1.	
	(1) To a mixture comprising 2.5 g of 1-acetyl-3-oxo-piperazine, 3.45 g of tri-	
25	ethylamine and 20 ml of anhydrous dioxane was added a solution of 3.71 g of trimethyl-	25
	chlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 17	
	hours and cooled to deposit triethylamine hydrochloride, which was then removed by	
	filtration. The filtrate was dropped at -40° to -30°C into a solution of 1.8 g of phos-	
	gene in 30 ml of anhydrous methylene chloride. After the dropping, the resulting mix-	20
30	ture was elevated in temperature, and reacted at room temperature for 30 minutes. Sub-	30
	sequently, the excess phosgene and the solvent were removed by distillation under	
	reduced pressure to obtain 3.5 g of pale brown, oily 4-acetyl-2-oxo-1-piperazino-	
	carbonyl chloride.	
•	IR (film) cm ⁻¹ : ν ₀₌₀ 1790, 1710, 1640	
35	(2) A suspension of 1.0 g. of 6-[D(-)-α-aminophenylacetamido] penicillanic	35
00	acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a	33
	pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to	
	0°C. Into the thus treated suspension was dropped a solution of 900 mg of the afore-	
	said 4-acetyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran at said	,
40	temperature over a period of 30 minutes. During this period, the pH of the suspension	40
	was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the	
	temperature of resulting mixture was elevated to 5° to 10°C, and the mixture was	
	reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by	
•	addition of triethylamine. After the reaction, the tetrahydrofuran was removed by	
45	reduced pressure distillation, and the residue was dissolved in a mixed solvent com-	45
	prising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted	
	to a pH of 1.5 to 2 by addition of dilute hydrochloric acid with ice-cooling, and then	
	the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of	
	ethyl acetate, and the resulting organic layer was combined with the aforesaid organic	
50	layer. The combined organic layer was washed with water, dried over anhydrous mag-	50 -
	nesium sulfate, and then ice-cooled. Into this organic layer was dropped a solution of	
	470 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate to deposit	
	white crystals. The deposited crystals were collected by filtration, washed with ethyl	÷
55	acetate and then dried to obtain 1.4 g of a sodium salt of $6-[D(-)-\alpha-(4-acety]-2-oxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid, m.p. 205°C (decomp.),$	
33	yield 94%.	55
	• •	
	IR (KBr) cm ⁻¹ : $\nu_{G=0}$ 1760 (lactam), 1600—1700 (—COO [©] , —CON<)	
	NMR: $[(CD_9)_2SO + D_2O] \tau$ values: 2.73 (5H), 4.35 (1H), 4.75 (2H), 5.75	
	(1H), 5.84 (2H), 6.42 (4H), 8.03 (3H), 8.52 (3H), 8.64 (3H)	
60	The shave-mentioned operation was consisted access that the state of a second	
00	The above-mentioned operation was repeated, except that the 4-acetyl-2-oxo-1-	60

piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 8, to obtain the respective objective compounds as shown in Table 8. The structure of each objective compound was confirmed by IR and NMR.

Table 8

Reactive derivative of compound of formula (III)	Objective compound
Cl_2CHCO-N_N-COCl	D(-)- C1_2CHCO-N N-CONHCHCONH S CH3 O
CH ₂ (CH ₂) ₄ CH ₂ CO-N 0-COC1	D(-)- CH ₃ (CH ₂) ₄ CH ₂ CO-N N-CONHCHCONH CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃
(H)-co-N N-coc1	D(-)- (H)-CO-N N-CONECHCONE S CH3 (CONECHCONE COONE (COONE COONE) (COONE COONE (COONE COONE) (COONE COONE) (COONE COONE) (COONE) (COONE COONE) (COONE) (COON

Table 8 (Cont'd)

CH ₃ CO-N N-COC1	$D(-)$ - CH_{2} O CH_{2} CH ₃ CH_{2} CH ₃ CO - N -CONHCHCONH O O O COONA O O O O O O O O O O
CH3SO2-N_N-COC1	D(-)- CH ₂ SO ₂ -N N-CONHCHCONH SCH ₃ CH ₂ CH ₃ SO ₂ -N COONB O O O O O O O O O O O O O O O O O O
сн ₃ (сн ₂) ₄ сн ₂ -и м-сос1	D(-)- $CH_{2}(CH_{2})_{4}CH_{2}-N$ O

cont'd

Table 8 (Cont'd)

c	D(-)-
CH ₂ (CH ₂) ₂ CH ₂ -N N-COC1	CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH CH ₃ CH ₃
	m.p. (decomp.) 158 - 161°C, yield 69 %
	D(-)-
CH ₂ (CH ₂) ₂ CH ₂ -N N-COCL	CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH S CH ₃ CH ₃ CH ₃ CONA
	m.p. (decomp.) 188 - 190°C, yield 81 %
	D(-)-
CH ₂ (CH ₂) ₆ CH ₂ -N N-COC1	CH2 (CH2) 6CH2-N N-CONHCHCONH SCH3
	m.p. (decomp.) 132 - 134°C, yield 63 %

. 으

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(Cont'd) Table 8

m.p. (decomp.) 218°C, yield 80 <u></u> (СН₃)3ССООСН2-N D(-)-(CH2)3CC00CH2-1

Example 2.

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acid in 30 ml of tetrahydrofuran containing 20% by volume of water which had been cooled to 0°C, a solution of 2.5 g of 4-acetyl-2-oxo-1-piperazinocarbonyl chloride in perature of the resulting mixed solution was elevated to 5° to 10° C, and the solution was reacted at room temperature for 2 hours while maintaining the pH thereof at 10.0washed with ethyl acetate and then dried to obtain 1.89 g of a sodium salt of $D(--)-\alpha$ (4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 115°C (decomp.), in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 to 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water and then dried over anhydrous magnesium sulfate. To this organic layer, a solution of 1.66 g of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate was added to Into a solution of 1.74 g of a sodium salt of $\mathrm{D}(-)$ -lpha-aminophenylacetic 5 ml of tetrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 1.0 to 12.0 by to 11.0 by addition of a 10% aqueous sodium hydroxide solution. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation. The residue was dissolved deposit white crystals. The deposited crystals were collected by filtration, sufficiently gradual addition of a 10% aqueous sodium hydroxide solution. Subsequently, the tem-

IR (KBr) cm⁻¹: v_{Gr} 0 1690, 1650—1600

mentioned sodium salt of D(-)- α -(4-acetyl-2-oxo-1-piperazinocarbonylamino) phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was colled to -20° to -15° C, and a solution of 286 mg of ethyl chlorocarbonate in 5 ml of anhydrous acetone was dropped into said mixture over a period of 5 minutes. Sub-To a suspension in 15 ml of anhydrous acetone of 833 mg of the above-

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sequently, the mixture was stirred at said temperature for 60 minutes. Into the thus treated mixture, a solution of 646 mg of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylene chloride was dropped at -40° to -30° C over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at -30° to -20° C for 60 minutes, at -20° to -10° C for 30 minutes, and at -10° to 0° C for 30 minutes. After the reaction, the organic solvent was removed by reduced pressure distillation. The residue was dissolved in a mixed solvent comprising 50 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate, and the ethyl acetate was removed by reduced pressure distillation. The residue was dissolved in 50 ml of acetone, and the resulting solution was mixed with a solution of 340 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of acetone with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with acetone and then dried to obtain 1.16 g of a sodium salt of 6 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] - penicillanic acid, m.p. 205°C (decomp.), yield 94%.

Example 3.

(1) To a mixture comprising 1.0 g of 1-palmitoyl-3-oxo-piperazine, 0.6 g of triethylamine and 20 ml of anhydrous dioxane was added a solution of 0.65 g of trimethylchlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 16 hours and cooled to deposit triethylamine hydrochloride, which was then removed by filtration. The filtrate was dropped at -40° to -30°C into a solution of 0.6 g of phosgene in 30 ml of anhydrous methylene chloride. After the dropping, the temperature of the resulting mixture was elevated and the mixture was reacted at room temperature for 30 minutes. Subsequently, the excess phosgene and the solvent were removed by reduced pressure distillation to obtain 1.1 g of pale yellow, oily 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride.

IR (film) cm⁻¹: $\nu_{C=0}$ 1740, 1660, 1640

(2) A suspension of 1.0 g of 6-[D(-)-\alpha-aminophenylacetamido] penicillanic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, a solution of 1.27 g of the aforesaid 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the suspension was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixture was elevated to 5° to 10°C, and the mixture was reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation, and the residue was dissolved in a mixed solvent comprising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted to a pH of 1.0 to 2.0 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water, and dried over anhydrous magnesium sulfate. This organic layer was concentrated under reduced pressure to remove the solvent, and the concentrate was charged into 10 ml of dissopropyl ether to deposit crystals. Thereafter, the crystals were collected by filtration to obtain 1.65 g of white crystals of $6-[D(-)-\alpha-(4-palmitoyl-2-oxo-1-piperazinocarbonylamino)$ phenylacetamido] penicillanic acid, m.p. 121—123°C (decomp.), yield 80%.

IR (KBr) cm⁻¹: $\nu_{C=0}$ 1770 (lactam), 1730 (—COOH), 1660—1630 (—CON<).

The above-mentioned operation was repeated, except that the 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 9, to obtain respective objective compounds as shown in Table 9. The structure of each objective compound was confirmed by IR and NMR.

Table 9

Reactive derivative of compound of formula (III)	Objective compound
сн ₃ (сн ₂)5сн ₂ со-м м-сос1	D(-)- CH ₃ (CH ₂) ₅ CH ₂ CO-N N-CONHOHOHOONH SCH ₃ O m.p. (decomp.) 151 - 153°C, yield 82 %
сн ₃ (сн ₂) ₃ сн ₂ со-и м-сос1	D(-)- CH ₂ (CH ₂) ₃ CH ₂ CO-N N-CONHCHCONH SCH ₃ CH ₃
о слсн ₂ со-м м-сост	D(-)- O C1CH2CO-M N-CONHCHCONH S CH2 CH2 O O O O O O O O O O O O O O O O O O O

Table 9 (Cont'd)

, (©)-co-w (w-cocı	O-co-n n-conhchconh rch ³ ch ³
	m.p. (decomp.) 120 - 124°C, yield 80 %
c1-\(\) c0-\(\) \(\) -c0c1	D(-)- C1-(-)- C1-(-
	m.p. (decomp.) 120 - 123°C, yield 91 %
о сн ₂ -О-со-и м-сос1	D(-)- OH3-O-CO-N N-CONHCHCONH S CH3 CH3-O-CO-N N-CONHCHCONH CH3
	m.p. (decomp.) 105 - 108°C, yield 88.6 %

Table 9 (Cont'd)

$\begin{array}{c} c_{H_{2}0} \\ c_{H_{3}0} \\ c_{H_{5}0} \end{array}$	CH_{20} CH_{50} $CH_{$
c1 ° c1-√O}-c0-N N-c0c1	D(-)- C1 O C1-CO-N M-CONHCHCONH S CH3 CH3 C1-C3 COOH CCOOH CCOOH CCOOH COOH COOH COOH
CH3CONECO-N N-COC1	D(-)- CH ₃ CONHCO-N N-CONHCHCONH S CH ₃ CH ₃ CONHCO-N N-CONHCHCONH O O O O O O O O O O O O O O O O O O O

cont'd.

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Table 9 (Cont'd)

D(-)- O-NHCO-N N-COCI m.p. (decomp.) 168 - 170°C, yield 83 D(-)- CH3CH2OCO-N N-COCI CH3CH2OCO-N N-CONHCHCONH SCH3 CH3CH2OCO-N N-CONHCHCONH SCH3 CH3CH2OCO-N N-COCH		
D(-	O-NHCO-N-COCI	D(-)- O-NHCO-N N-CONHCHCONH SCH3 O-NHCO-N N-CONHCHCONH CH2
		m.p. (decomp.) 168 - 170°C, yield 83.3 %
m.p. (aecomp.) ab c. ylela yl %	CH20CO-N -COC1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

dimethylformamide was added 2.7 g of a sodium hydride (purity 53%) with ice-cooling and the resulting mixture was reacted at room temperature for 1 hour. Subsequently, the mixture was incorporated with 7.1 g of methyl iodide and reacted for 10 hours. After the reaction, the dimethylformamide was removed by reduced pressure distillation to obtain 1-formyl-4-methyl-3-oxo-piperazine. This piperazine was dissolved in 70 ml of a 50% aqueous acetone solution containing 2.2 g of sodium hydroxide, and the resulting solution was reacted at room temperature for 3 hours. Thereafter, the solvent quently, the residue was subjected to reduced pressure distillation to obtain 5.2 g of 1-methyl-2-oxo-piperazine, b.p. 104°C/4 mmHg, yield 91%.

(2) Into a solution of 1.9 g of phosgene in 20 ml of anhydrous dioxane was dropped at 10°C 20 ml of an anhydrous dioxane solution containing 2.0 g of 1-methyl-2-oxo-piperazine and 1.95 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. The deposited crystals were removed by filtration, and the filtrate was concentrated to dryness to obtain 3.0 g of pale yellow, was removed by distillation under reduced pressure, and the residue was charged into acetone to deposit insolubles. The insolubles were separated by filtration, and the acetone was removed from the filtrate by distillation under reduced pressure. Subse-S 2 15

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'n

IR (film) cm⁻¹: vo=01710, 1630

oily 4-methyl-3-oxo-1-piperazinocarbonyl chloride

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5	(3) A suspension of 4.0 g of 6-[D(-)-\alpha-aminophenylacetamido] penicillanic acid in 40 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, 10 ml of a tetrahydrofuran solution containing 2.2 g of the aforesaid 4-methyl-3-oxo-1-piperazinocarbonyl chloride was dropped. During this period, the pH of the suspension was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was elevated to 10° to 15°C, after	. 5
10	which the mixture was further reacted at said temperature for 90 minutes while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 30 ml of water. The resulting solution was washed with ethyl acetate, and then the aqueous layer was separated off. This aqueous layer was ice-cooled and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white	10
15	crystals. The deposited crystals were collected by filtration, washed several times with a small amount of water, dried, and then dissolved in 100 ml of acetone. To the resulting solution was added 1.9 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals, which were then collected by filtration to obtain 5.4 g of a sodium salt of $6-[D(-)-\alpha-(4-\text{methyl-}3-\text{oxo-}1-\text{piperazinocarbonylamino})$ phenylacet-	15
20	amido] penicillanic acid, m.p. 195°C (decomp.), yield 92%. IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1760 (lactam), 1600—1660 (—CON<, —COO \ominus) NMR [(CD ₃) ₂ SO+D ₂ O] τ values: 2.62 (5H), 4.48 (1H), 4.56 (2H), 5.97 (3H), 6.63—6.39 (4H), 7.13 (3H), 8.46 (3H), 8.55 (3H)	20
25	The above-mentioned operation was repeated, except that the 4-methyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 10, to obtain respective objective compounds as shown in Table 10. The structure of each objective compound was confirmed by IR and NMR.	25

Table 10

Objective compound	$D(-)-$ $CH_{2}(CH_{2})_{2}CH_{2}-N$ O	D(-)- O CH3CH2-N N-CONHCHCONH S CH3 CH3 O O O O O O O O O O O O O O O O O O O	D(-)-O O O O O O O O O O O O O O O O O O O
Reactive derivative of compound of formula (III)	о сн ₃ (сн ₂) ₂ сн ₂ -м м-сос1	CH ₂ CH ₂ -N N-COC1	(сн ₃) ₂ сн-и м-сос1

Table 10 (Cont'd)

он ₃ (сн ₂) ₃ сн ₂ -м м-сос1	D(-)- 0 CH3(CH2)3CH2-N N-CONHCHCONH
о СН3)2СНСН2СН2-N_)и-СОС1	D(-)- (CH ₂) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₃ CH ₂ -N CH ₃ (CH ₃) ₂ CHCH ₃ CH ₂ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₃ CHCH ₃ -N CH ₃ (CH ₃) ₄ CHCH ₄ -N CH ₃ (CH ₃) ₄ CHCH ₄ -N CH ₃ (CH ₃) ₄ CHCH ₄ -N CH ₄ (CH ₃) ₄ CHCH ₄ -N CH ₄ (CH ₃) ₄ CHCH ₄ -N CH ₄ (CH ₃) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CHCH ₄ -N CH ₄ (CH ₄) ₄ CH
сн ₃ (сн ₂) ₂ сн ₂ -м м-сос1	$D(-) CH_{2}$ $CH_{2}-M$ $M-CONHCHCONH$ CH_{2} $CH_{2}-M$ $CH_{2}-M$ $COONa$ O

cont'd

Table 10 (Cont'd)

D(-)- $CH_{3}(CH_{2})_{2}CH_{2}-N$ CH_{3} CH_{4} CH_{3} CH_{4} CH_{4} CH_{4} CH	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH	D(-)- O CH2-N N-CONHCHCONH S CH3 O CH2-N N-CONHCHCONH CH2 O CH2-N N-CONHCHCONH CH3 O CH2-N N-CONHCHCONH CH3
он ₃ (сн ₂) ₂ сн ₂ -м м-сос1 сн ₃	сн ₃ (сн ₂) ₂ сн ₂ -и и-сос1	0 CD-cH2-N—coc1

cont'd -

Table 10 (Cont'd)

о носн ₂ сн ₂ -м м-сос1	D(-)- 0 HOCH ₂ CH ₂ -N N-CONFCHCONH \longrightarrow S CH ₂ O 0 m.p. (decomp.) 100 - 105°C, yield 67 %
CH ₃ CO-N -COC1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
O CH ₃ H ₂ NCO-N N-COCL	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

cont'd

Table 10 (Cont'd)

O HW W-COC1	HN N-CONHCHCONH S CH2
)	(O) 0 COONB m.p. (decomp.) 213°C, yield 70 %
0 CH ₃ HN N-COC1 CH ₃	D(-)- 0 CH3 HN N-CONHCHCONH CH3 CH3 CH3 0 CH5 0 0 CH5 0 0 CH5 CH5 0 0 CH5 0 0 CH5 0 0 CH5 0 0 CH5
о ни ју-сост сн ₃	D(-)- O HN N-CONHCHCONH CH_{2} CH_{3} CH_{2} CH_{3} CH_{2} CH_{3} CH_{3} CH_{3} CH_{2} CH_{3} CH_{4} CH_{5}

Table 10 (Cont'd)

O CH2COOCH2CH3	D(-)- O CH2COOCH2CH3 HN N-CONHCHCONH CH2 O CH2 O CH2COOLB O CH2COOLB O COONB O COONB O COONB
O CH ₂ HN N-COC1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
(1) A solution of 1.0 g o	Example 5. (1) A solution of 1.0 g of a sodium salt of D(-)-\alpha-aminophenyl acetic acid in

(1) A solution of 1.0 g of a sodium salt of D(—)-c-aminophenyl acetic acid in 20 ml of terrahydrofuran containing 20% by volume of water was cooled to 0° to 5°C. To this solution was added 1.2 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the solution was maintained at 11.0 to 12.0 by gradual addition of a 10% aqueous sodium hydroxide solution. The solution was reacted at said temperature for 1 hour, and the temperature thereof was elevated to 5° to 10°C, after which the mixture was further reacted at said temperature for 2 hours, while maintaining the pH thereof at 10.0 to 11.0 by addition of a 10% aqueous sodium hydroxide solution. After the reaction, tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate. The resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was further extracted with 50 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was added 0.9 g of a sodium salt

	of 2-ethylhexanoic acid to deposit white crystals. The deposited crystals were collected by filtration and then dried to obtain 1.26 g of white crystals of a sodium salt of $D(-) - \alpha - (2 - \text{methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid, m.p. 215°C (decomp.), yield 70%.	
5	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1650—1590	5
•	(2) To a suspension in 15 ml of anhydrous acetone of 1.0 g of the above-mentioned sodium salt of $D(-)-\alpha$ -(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was cooled to -20° to -15° C, and a solution of 380 mg of ethyl chlorocarbonate in 5 ml of	
10	annydrous acetone was dropped into said mixture over a period of 5 minutes. Subsequently, the mixture was stirred at said temperature for 60 minutes, and then cooled to -40° to -30°C. Into the thus treated mixture was dropped a solution of 960 mg of a triethylamine salt of 6-aminopenicillanic acid in 10 ml of anhydrous methylene chloride over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at -30°	. 10
15	to -20° C for 60 minutes, at -20° to -10° C for 30 minutes, and at -10° to 0° C for 30 minutes. After the reaction, the organic solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic	15
20	layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate. To this organic layer was added 0.5 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, and then dried to obtain 1.39 g of a sodium salt of $6-[D(-)-\alpha-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid, m.p.$	20
25	In the same manner as above, 2.0 g of a sodium salt of $6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{propionamido}] \text{penicillanic acid, m.p. 195°C (decomp.), yield 86%, was obtained from 1.59 g of a sodium salt of D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{propionic acid and } 1 - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	25
30	1.59 g of a triethylamine salt of 6-aminopenicillanic acid. IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1760 (lactam), 1680—1600 (—CON<, —COO®)	30
	Example 6.	٠
35	(1) Into a solution of 0.5 g of phospene in 10 ml of anhydrous dioxane was dropped at 10°C 10 ml of anhydrous dioxane containing 0.56 g of 1-allyl-2-oxo-piperazine and 0.5 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. Subsequently, the deposited crystals were collected by filtration, and the filtrate was concentrated to dryness to obtain 800 mg of pale yellow, oily 4-allyl-3-oxo-1-piperazinocarbonyl chloride.	35
	IR (film) cm ⁻¹ : $\nu_{C=0}$ 1720, 1640	
40	(2) A suspension of 1.4 g of 6-[D(-)-α-aminophenylacetamido] penicillanic acid in tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension was dropped 10 ml of a tetrahydrofuran solution containing 800 mg of the aforesaid 4-allyl-3-oxo-1-piperazinocarbonyl chloride. During	40
45	of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was then elevated to 10° to 15°C, after which the mixture was further reacted at said temperature for 90 minutes while main-	45
. 50	taining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water. The resulting solution was washed with ethyl acetate, and the aqueous layer was then separated off. This aqueous layer was ice-cooled and adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals.	50
55	then deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 1.8 g of $6-[D(-)-\alpha-(4-allyl-3-oxo-1-piperazinocarbonylamino)-phenylacetamido] penicillanic acid, m.p. 92°C (decomp.), yield 90%.$	55
60	IR (KBr) cm ⁻¹ : $v_{C=0}$ 1760 (lactam), 1720—1620 (—COOH, —CON<) The above-mentioned operation was repeated, except that the 4-allyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 11, to obtain respective objective compounds as shown in Table 11. The structure of each objective compound was confirmed by IR and NMR.	60

Table 11

Objective compound	D(-)- O CH2=CHCH-N N-CONHCHCONH CH2 CH3 CH2=CHCH-N N-CONHCHCONH CH3 CH2 CH2 CH2 CH2 CH2 CH2 CH3 COOH CH2 COOH CH2 CH2 COOH CH2 COOH COOH CH2 COOH CH2 COOH CH2 COOH CH2 COOH CH2 COOH CH2 COOH COOH CH2 COOH CH2 COOH COO	D(-)- 0 CH2=CCH2-N N-CONHCHCONH CH2 CH3 CH3 CH2=CCH2-N N-CONHCHCONH CH2 CH3 CH3 m.p. (decomp.) 90°C, yield 85 %	D(-)- CH3CH O CH2CH CH2-N N-CONHCHCONH S CH3 CH3 CH3 (trans-) O (trans-) O 0 (trans-) O 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Reactive derivative of compound of formula (III)	CH2=CHCH-N N-COCL	сн ₂ =ссн ₂ -м м-сост сн ₃	CH3CH O HCCH2-N N-COCL (trans-)

Table 11 (Cont'd)

сн ₃ (сн ₂) ₄ сн ₂ -м м-сос1	D(-)- CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH CH ₃ CH ₃ CH ₃ CH ₂ CH ₃
он ₃ (сн ₂) ₅ сн ₂ -м м-сос1	D(-)- CH ₃ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH SCH ₃ O m.p. (decomp.) 120°C, yield 94 %
сн ₃ (сн ₂) ₆ сн ₂ -м м-сос1	D(-)- CH ₃ (CH ₂) ₆ CH ₂ -N N-CONHCHCONH B CH ₃ CH ₃ COOH O O O O O O O O O O O O O O O O O O

Table 11 (Cont'd)

•	
сн ₃ (сн ₂) ₁₀ сн ₂ -м м-сос1	D(-)- CH ₂ (CH ₂) ₁₀ CH ₂ -N N-CONHCHCONH SCH ₃ CH ₃ (CH ₂) ₁₀ CH ₂ -N N-CONHCHCONH COOH O
E)-N N-cocı	D(-)- $(H)^{O}$
O-NHCO-N N-COCI	D(-)- O CONHCHCONH S CH3 COOH COOH COOH COOH COOH COOH COOH

S

Table 11 (Cont'd)

- 128°C, yield 79.5 (decomp.) 125 0 m.p. D(-)-

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Using 0.63 g of 6-[D(-)- α -aminophenylacetamido]penicillanic acid and 600 mg of a hydrochloride of 4-(N-morpholinomethyl)-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Example 6 was repeated to obtain 0.63 g of 6- {D(-)- α -[4 - (N - morpholinomethyl) - 3 - oxo - 1 - piperazinocarbonylamino]phenylacetamido)penicillanic acid, m.p. 85°C (decomp.), yield 60%.

S

IR (KBr) cm⁻¹: v₀₌₀: 1770 (lactam), 1600—1680 (—COO[⊕], —CON<)

2

Using 5.0 g of a hydrochloride of pivaloyloxymethyl ester of 6-[D(--)-\alpha-amino-phenylacetamido]penicillanic acid and 1.94 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Bxample 6 was repeated to obtain 5.2 g of a pivaloyloxymethyl ester of 6-[D(--)-\alpha-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 140°C (decomp.), yield 80%.

15 IR (KBr) cm⁻¹: v₀₌₀ 1740—1770 (lactam, ester) 1630—1670 (—CON<) Example 9. 15

triethylamine and 100 ml of anhydrous tetrahydrofuran was dropped 6.0 g of trimethylamine and 100 ml of anhydrous tetrahydrofuran was dropped 6.0 g of trimethylchlorosilane with stirring at room temperature. After the dropping, the resulting mixture was reacted at said temperature for 2 hours to deposit triethylamine hydrochloride. The deposited hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into 100 ml of an anhydrous tetrahydrofuran solution containing 10.0 g of phosgene. After completion of the dropping, the resulting mixture was stirred at 10°

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•	to 15°C for 3 hours to terminate the reaction. Subsequently, the tetrahydrofuran and the excess phosgene were removed by distillation under reduced pressure to obtain 11.0 g of oily 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride.	
5	(2) A suspension of 17.5 g of 6-[D(-)-α-aminophenylacetamido]penicillanic acid in 200 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethyl amine with stirring at 10° to 15°C to form a homogeneous solution. Into this solution was dropped a solution of 11.0 g of the	5
10	aforesaid 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride in 30 ml of tetrahydrofuran at 0°C over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C and the solution was further reacted for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After completion of the reaction, the tetrahydrofuran was removed	10
15	by distillation under reduced pressure. To the residue was added 100 cc of N hydro- chloric acid at 0° to 10°C, and the resulting mixture was stirred for 30 minutes to deposit white crystals. The deposited crystals were collected by filtration, and again suspended in water. The resulting aqueous suspension was adjusted to a pH of 8.0 by	15
20	gradual addition of triethylamine at 5° to 10°C, and then freed from insolubles by filtration. The filtrate was adjusted to a pH of 1.5 by gradual addition of N-hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 21.2 g of 6- $[D(-)-\alpha-(4-\text{acetyl-2,5-dioxo-1-piperazino-carbonylamino})$ phenylacetamido]penicillanic acid, b.p. 162—164°C (decomp.), yield 80%.	20
25	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1770 (lactam), 1730—1660 (—COOH, —CON<) NMR ((CD _a) ₂ CO) τ values: 0.23 (1H), 2.65 (5H), 4.26 (1H), 4.33—4.63 (2H), 5.38 (4H), 5.68 (1H), 7.55 (3H), 8.47 (3H), 8.53 (3H)	25
30	The above-mentioned operation was repeated, except that the 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 12, to obtain respective objective compounds as shown in Table 12. The structure of each objective compound was confirmed by IR and NMR.	30

Table 12

Reactive derivative of compound of formula (III)	Objective compound
0 -co-w_w-coc1	D(-)- O-co-N N-conhchconh CH3 O-co-N N-conhchconh CH3 O O COOH m.p. (decomp.) 88°C, yield 60 %
CH3-N N-COCI	D(-)- O CH ₃ -N N-CONHCHCONH S CH ₃ O O O COOH m.p. (decomp.) 179 - 181°C, yield 83 %
CO-CH2-N N-coc1	D(-)- O-CH2-N N-CONHCHCONH SCH3 OOOH OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO

cont'd -

Table 12 (Cont'd)

O (H) HIN N-COC1	D(-)- 0 (H) HN N-CONHCHCONH S CH3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
о НИ N-сос1 о	D(-)- N-CONHCHCONH N-CONHCHCONH O O O N-D. (decomp.) 176 - 181°C, yield 84.4 %
HN N-COC1	D(-)- 0 CH ₂ HN N-CONHCHCONH S CH ₂ 0 O CH ₃ m.p. (decomp.) 148 - 151°C, yield 92 %

Table 12 (Cont'd)

O (H) O-ch2-N N-coc1	$\begin{array}{c} D(-)^{-} \\ \bigcirc \\ \bigcirc \\ -CH_{2} - N \\ \bigcirc \\$
Cl3CCH2OCO-N N-COC1	D(-)- Cl ₃ CCH ₂ OCO-N N-CONHCHCONH S CH ₃ Cl ₃ CCH ₂ OCO-N N-CONHCHCONH O O M.p. (decomp.) 120 - 125°C, yield 92 %
O-CH2-N N-COC1	D(-)- OCH2-N N-CONHCHCONH S CH3 OCH2-N N-CONHCHCONH CH3 OCH2-N N-CONHCHCONH CH3 OCH3 OCH2-N N-CONHCHCONH S COOH OCH3

	Example 10.	
•	(1) A suspension of 8.0 g of $D(-)-\alpha$ -aminophenyl acetic acid in 80 ml of tetrahydrofuran was adjusted to a pH of 11.5 by gradual addition of a N sodium hydroxide	
5	solution with stirring to form a homogeneous solution. This solution was cooled to 0°C, and 15 ml of a tetrahydrofuran solution containing 11 g of 4-acetyl-2,5-dioxo-1-piper-	• 5
J	azinocarbonyl chloride was dropped at said temperature into said solution over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at	
	10.5 to 11.0 by gradual addition of a N sodium hydroxide solution. Subsequently, the	•
10	temperature of the resulting mixed solution was elevated to 5° to 10°C, and the mixture was further reacted for 1 hour, upon which $D(-)-\alpha$ -aminophenylacetic acid	10
10	deposited. After completion of the reaction, the deposited acid was separated by filtra-	10
	tion, and the filtrate was concentrated under reduced pressure to remove tetrahydro- furan. The residue was dissolved in a mixed solvent comprising 10 ml of water and	
15	80 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was	15
15	separated off, dried over anhydrous magnesium sulfate, and then charged into 100 ml	. 13
-	of an ethyl acetate solution containing 8.3 g of sodium 2-ethylhexanoate to deposit crystals. The deposited crystals were collected by filtration, washed with acetone, and	
20	then dried over P_2O_5 to obtain 7.9 g of a sodium salt of $D(-)-\alpha$ -(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 104°C (decomp.), yield 42%.	20
20		
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1690—1650, 1600—1590	
	(2) To a suspension in 25 ml of anhydrous acetone of 1.75 g of the aforesaid sodium salt of $D(-)-\alpha-(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)$ phenylacetic	
	acid was added 20 mg of N-methylmorpholine, and the resulting mixture was cooled to	
25	-20° to -15°C. Into this mixture was dropped a solution of 0.57 g of ethyl chloro- carbonate in 5 ml of anhydrous acetone over a period of 5 minutes, and the mixture was	25
	stirred at said temperature for 60 minutes. Subsequently, a solution of 1.29 g of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylenechloride	
20	was dropped into said mixture at -40° to -30°C over a period of 10 minutes. The	
30	temperature of the resulting mixture was elevated from -30°C to 0°C, and the mixture was then reacted at said temperature for about 2 hours. After the reaction, the sol-	30
	vent was removed by distillation under reduced pressure. The residue was charged into 30 ml of water, and the resulting mixture was freed from insolubles by filtration with	
	ice-cooling. The filtrate was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydro-	
35	chloric acid to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, and then dried to obtain 2.34 g of $6-[D(-)-\alpha-(4-acety)]$	35
	2,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 162—164°C (decomp.), yield 90%.	
	In the same manner as above, 530 mg of 6- $[D(-)-\alpha-(4-benzyl-2,2-pentamethyl-$	
40	ene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 95—100°C, yield 82.68%, was obtained from 450 mg of $D(-)-\alpha$ -(4-benzyl-2,2-penta-	40
	methylene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid and 320 mg of a triethylamine salt of 6-amino-penicillanic acid.	
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1770 (lactam), 1700—1660 (—COOH, —CON<)	
45	Example 11. (1) Into a mixture comprising 8 g of a diethyl ester of oxalic acid and 8 ml of	45
	ethanol was dropped at room temperature 4.4 g of N-ethyl ethylenediamine. The result-	
	ing mixture was allowed to react for 3 hours, and then heated to remove the ethanol. Subsequently, the residue was recrystallized from 10 ml of dioxane to obtain 5.4 g of	•
50	1-ethyl-2,3-dioxo-piperazine, m.p. 124°C, yield 76.0%. (2) To a suspension of 0.71 g of the above-mentioned 1-ethyl-2,3-dioxo-piper-	50
	azine in 15 ml of anhydrous dioxane were added with stirring 0.70 g of trimethylsilyl	•
	chloride and 0.83 ml of triethylamine. The resulting mixture was stirred at room temperature for 20 hours to deposit triethylamine hydrochloride. This hydrochloride was	•
55	separated by filtration, and the filtrate was dropped at 5° to 10°C into a solution of 0.70 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting	.55
	mixture was reacted at 5° to 10°C for 30 minutes and at room temperature for 2 hours,	
	and then the solvent was removed by distillation under reduced pressure to obtain 1.0 g of pale yellow crystals of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.	
	• • • • • • • • • • • • • • • • • • • •	

IR (KBr) cm⁻¹: $\nu_{G=0}$ 1780, 1660

5	(3) A suspension of 1.75 g of 6-[D(-)-α-aminophenylacetamido]penicillanic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and then 7 ml of an anhydrous tetrahydrofuran solution containing 1.0 g of the aforesaid 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into the solution. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted at said temperature for 30 minutes and then at 5° to 10°C for 1 hour,	5
10	while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous	10
15	layer was again added 50 ml of ethyl acetate, and the resulting mixture was adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, sufficiently washed with water, and then dried over anhydrous magnesium sulfate. Into the thus treated layer was dropped	15
	10 ml of an ethyl acetate solution containing 0.83 g of sodium 2-ethyl-hexanoate to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with ethyl acetate, washed with diethyl ether, and then dried to obtain 2.4 g of a sodium salt of $6-[D(-)-\alpha-(4-\text{ethyl-}2,3-\text{diox}o-1-\text{piperazinocarbonylamino})$ phenyl-	20
20	acetamido] penicillanic acid, m.p. 183—185°C (decomp.), yield 89%. IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1765 (lactam), 1720—1670 (—CON<), 1600 (—COO ^{\ominus}) NMR ((CD ₃) ₂ SO+D ₂ O) τ values: 2.62 (5H), 4.31 (1H), 4.50 (1H), 4.70 (1H), 6.05 (1H), 6.35—6.65 (6H), 8.49 (3H), 8.60 (3H), 8.91 (3H)	20
25	The above-mentioned operation was repeated, except that the 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 13, to obtain respective objective compounds as shown in Table 13. The structure of each objective compound was confirmed by IR and NMR.	25

Table 13

Reactive derivative of compound of formula (III)	Objective compound
CH3-N N-COC1	$D(-)-0$ $CH_{3}-N$ $M-CONHCHCONH$ $CH_{3}-N$ $COON_{0}$ $COON_{0}$ $M.p. (decomp.) 170°C, yield 84 %$
CH ₃ CH ₂ CH ₂ -N N-COC1	D(-)- CH ₃ CH ₂ CH ₂ -N -CONHCHCONH S CH ₃ CH ₃ CH ₂ -N CONHCHCONH CH ₃ O COONa m.p. (decomp.) 170°C, yield 86 %
оо сн ₃ (сн ₂) ₂ сн ₂ -мососі	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH CH ₃

Table 13 (Cont'd)

(CH ₃) ₂ CH-N N-COC1	D(-)- 0 0 (CH ₃) ₂ CH-N N-CONHCHCONH CH ₃ CH ₃ (CH ₃ COONa Occomb.) 186°C, yield 85 %
сн ₃ соосн ₂ сн ₂ -м м-сос1	D(-)- CH ₂ COOCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ COOCH ₂ CH ₂ -N N-CONHCHCONH COONB m.p. (decomp.) 175°C, yield 79 %
СН2=СНСН2-И N-СОС1	D(-)- CH2=CHCH2-N N-CONHCHCONH S CH3 CH2=CHCH2-N N-CONHCHCONH CCOONB m.p. (decomp.) 198 - 200°C, yield 75 %

Table 13 (Cont'd)

0 - v √ v - coc1	D(-)- O-N N-CONHCHCONH SCH3 O O COONA m.p. (decomp.) 185 - 187°C, yield 88 %
Clch2ch2-N—cocl	D(-)- C1CH2CH2-N N-CONHCHCONH S CH3 C1CH2CH2-N N-CONHCHCONH O 0 0 0 0 0 0 0 0 0
0 0 0 0 0H3CH2-N N-COC1 CH3	D(-)- CH_3CH_2-N CH_3CH_2-N CH_3 C

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Table 13 (Cont'd)	$D(-)-$ $CH_{2}-N$ $CH_{3}-N$ CH_{3} $M.P. (decomp.) 177 - 178^{0}C, yield 79 %$
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30 ml of terrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 10 ml of a tetrahydrofuran solution containing 1.2 g of A suspension of 1.4 g of $6-[D(-)-\alpha$ -aminophenylacetamido] penicillanic acid in gradual addition of triefhylamine. Subsequently, the resulting mixed solution was reacted at said temperature for 30 minutes and then at 10° to 15°C for 90 minutes, 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into said solution. During this period, the pH of the reaction solution was maintained at 7.5 to 8.5 by while maintaining the pH thereof at 7.5 to 8.5. After the reaction, the tetrahydrofuran

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was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Thereafter, the

layer was further added 30 ml of ethyl acetate, and the resulting mixture was adjusted ethyl acetate layer was separated off, sufficiently washed with water, dried over mag-

The residue was crystallized by addition of disopropyl ether to obtain 1.8 g of crystals of 6- $[D(-)-\alpha-(4-n-pentyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylnesium sulfate, and then freed from the solvent by distillation under reduced pressure IR (KBr) cm⁻¹: v₀₌₀ 1770 (lactam), 1720—1660 (—CON<, —COOH) NMR ((CD₂)₂SO+D₂O) τ values: 2.62 (5H), 4.31 (1H), 4.51—4.69 acetamido] penicillanic acid, m.p. 96°C (decomp.), yield 80.5%.

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The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-l-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 14, to obtain respective objective compounds as shown in Table 14. The structure of each objective compound was confirmed by IR and NMR 25

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Objective compound	D(-)- CH ₂ (CH ₂) ₄ CH ₂ -N -CONHCHCONH - S CH ₃ CH	D(-)- CH ₂ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH SCH ₂ CH ₃ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH m.p. (decomp.) 92°C, yield 88.5 %	D(-)- OH3 (CH2)6CH2-N N-CONHCHCONH CH2 CH3 (CH2)6CH2-N N-CONHCHCONH CH2 OOO OO m.p. (decomp.) 95°C, yield 79.8 %
Reactive derivative of compound of farmula (III)	оо сн ₃ (сн ₂) ₄ сн ₂ -и и-сос1	ооо сн ₃ (сн ₂) ₅ сн ₂ -м м-сос1	OH2(CH2)6CH2-N N-COC1

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(Cont'd) Table 14

	D(-)-
CH ₂ CH ₂ -N N-CSC1	CH ₂ CH ₂ -N N-CSNHCHCONH S CH ₃ (O) CH ₂ CH ₃
	m.p. (decomp.) 80 - 82°C, yield 95 %

the same operation as in Example 11 was repeated to obtain 1.2 g of a sodium salt of $6 - [D(-) - \alpha - (4 - methyl - 2.3 - dioxo - 1 - piperazinocarbonylamino) - phydroxyphenylacetamido] penicillanic acid, m.p. 170—172°C (decomp.), yield 75%.$ Using 1.7 g of a triethylamine salt of $6-[D(-)-\alpha$ -amino-p-hydroxyphenylacetamido] penicillanic acid and 0.7 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride,

IR (KBr) cm⁻¹: v₀₌₀ 1760 (lactam), 1710—1660 (—CON<), 1600 (—COO[⊕]) NMR ((CD₈)₂SO) τ values: 2.8—3.3 (4H), 4.45 (1H), 4.65 (2H), 6.05 (1H), 6.2 (4H), 6.97 (3H), 8.48 (3H), 8.60 (3H)

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In the same manner as above, a sodium salt of 6-[D(—)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]penicillanic acid, m.p. 175°C (decomp.), yield 72%, was obtained from 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride and a triethylamine salt of $6-[D(-)-\alpha$ -amino-p-hydroxyphenylacetamido]penicillanic acid.

chloride with ice-cooling, and the mixture was reacted at room temperature for 2 hours. After the reaction, the solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 20 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 2 by addition of dilute hydrochloric acid. Subsequently, the organic layer was separated off, washed with water, washed with a 2% aqueous sodium hydrogenocarbonate solution, washed with water, To a solution of 0.8 g of a phthalide ester of 6-[D(-)-a-aminophenylacetamido]penicillanic acid in 10 ml of tetrahydrofuran was added 0.25 ml of triethylamine. Into the resulting mixture was dropped 0.32 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl Example 14. ន 23

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dried over magnesium sulfate, and then concentrated to a liquid amount of about 2 ml. To the concentrate was added 20 ml of disopropyl ether to deposit crystals, which were then collected to obtain 0.95 g of crystals of a phthalide ester of $6-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido] penicillanic acid, m.p. 157—160°C (decomp.), yield 90.0%.

IR (KBr) cm⁻¹: $v_{G=0}$ 1780 (lactam), 1715 (ester), 1680 (—CON<) NMR ((CD₈)₂CO₁+D₂O) τ values: 2.12 (4H), 2.40 (1H), 2.58 (5H), 4.25—4.60 (3H), 5.45 (1H), 5.85—6.42 (4H), 6.90 (3H), 8.50 (6H)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 15, to obtain respective objective compounds as shown in Table 15. The structure of each objective compound was confirmed by IR and NMR.

Table 15

Reactive derivative of compound of formula (III)	Objective compound
CH3CH2-N N-COCI	D(-)- CH3CH2-N N-CONHCHCONH SCH3 O CH3 CH3CH2-N N-CONHCHCONH
	m.p. (decomp.) LUB - LLO'C, yield 90 %
0 0 (СН ₃) ₂ СН-N N-СОС1	D(-)- (CH ₃) ₂ CH-N N-CONHCHCONH S CH ₃ O O O O O O O O O O O O O O O O O O O
СН3 (СН2) 2 СН2 - N N-СОС1	D(-)- CH3(CH2)2CH2-N N-CONHCHCONH SCH3 0 CH3(CH2)2CH2-N 113-115°C, yield 88 %

Example 15. A solution of 0.86 g of a hydrochloride of methoxymethyl ester of 6-[D(-)-aaminophenylacetamido penicillanic acid in 15 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine at 5 0° to 5°C. Into this solution, a solution of 0.38 g of 4-methyl-2,3-dioxo-1-piperazino-5 carbonyl chloride in 10 ml of tetrahydrofuran was dropped over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted for 30 minutes, while maintaining the pH thereof at 7.5 to 8.0. After completion of the reac-10 tion, the tetrahydrofuran was removed by distillation under reduced pressure. The 10 residue was dissolved in a mixed solvent comprising 50 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to form crystals. The thus formed crystals 15-15 were washed with diethyl ether to obtain 0.9 g of a methoxymethyl ester of 6-[D(-)α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetamido] penicillanic acid, m.p. 111—115°C (decomp.), yield 82.5%. IR (KBr) cm⁻¹: $\nu_{C=0}$ 1780 (lactam), 1740 (ester), 1700—1660 (—CON<) NMR ((CD_s)₂CO) τ values: 0.15 (1H), 2.0 (1H), 2.67 (5H), 4.3—4.5 (3H), 4.75 (2H), 5.7 (1H), 6.55 (4H), 6.97 (3H), 7.25 (3H), 8.84 (3H), 8.60 (3H) 20 20 The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of com-25 25

pounds of formula (III) shown in Table 16, to obtain respective objective compounds as shown in Table 16. The structure of each objective compound was confirmed by IR and NMR.

Table 16

	Objective compound	D(-)- CH ₃ CH ₂ -N N-CONHÇHCONH CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₃ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃ C	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH S CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH O O O O O O O O O O O O O O O O O O O	D(-)- OOO (CH ₃) ₂ CH-NN-CONHCHCONH OOO OOO m.p. (decomp.) 93 - 95°C, yield 82.5 %
1	Reactive derivative of compound of formula (III)	CH ₂ CH ₂ -N-COC1	о о сн ₃ (сн ₂) ₂ сн ₂ -и и-сос1	(CH ₃) ₂ CH-N N-COC1

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Table 16 (Cont'd)

D(-)-	CH ₂ (CH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₂ CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₂) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₂ -N N-CONHCHCONH CH ₃ (OH ₃) ₆ CH ₃ -N N-CONHCHCONH CH ₃	m.p. (decomp.) 70 - 74°C, yield 74.4 %
	O O CH2 (CH2) 6 CH2 - N N-COCI	

Using 1.5 g of a hydrochloride of pivaloyloxymethyl ester of $6-[D(-)-\alpha$ -aminophenylacetamido]penicillanic acid and 0.6 g of 4-methyl-2,3-dioxo-1-piperazino-carbonyl chloride, the same operation as in Example 15 was repeated to obtain a pivaloyloxymethyl ester of $6-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 108—111°C (decomp.), yield 75%.$

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IR (KBr) cm⁻¹: v₀₌₀ 1780 (lactam), 1750 (ester), 1710-1660 (-CON<)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 17, to obtain respective objective compounds as shown in Table 17. The structure of each objective compound was confirmed by IR and NMR.

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Reactive derivative of compound of formula (III)	Objective compound
CH ₃ CH ₂ -N N-COC1	D(-)- $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{3}$ $CH_{3}CH_{2}$ $CH_{3}CH_{3}$ CH_{3
сн ₃ (сн ₂) есн ₂ м–сост	D(-)- CH3(CH2)6CH2-N N-CONHCHCONH S CH3 CH3 CH3(CH2)6CH2-N N-CONHCHCONH CH2 O 0 0 N.p. (decomp.) 72 - 75°C, yield 72 %

Using 0.81 g of a hydrochloride of β -piperidinoethyl ester of 6-[D(-)- α -aminophenylacetamido)penicillanic acid and 0.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.75 g of a β -piperidinoethyl ester of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 166—169°C (decomp.), yield 78%.

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IR (KBr) cm⁻¹: v₀₌₀ 1780 (lactam), 1740 (ester), 1710—1670 (—CON<) NMR (CDCl₈) τ values: 2.7 (5H), 4.3—4.6 (3H), 5.7 (1H), 5.75 (2H), 6.0 (2H), 6.4 (2H), 6.9 (3H), 7.45 (2H), 7.6 (4H), 8.5 (12H)

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The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a β -piperidinoethyl ester of 6-[D(-)- α -(4-n-octyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 110—115°C (decomp.), yield 73.58%.

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5	Example 18. Using 0.93 g of a hydrochloride of β -morpholinoethyl ester of 6-[D(-)- α -aminophenylacetamido] penicillanic acid and 0.39 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.8 g of a β -morpholinoethyl ester of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonyl-amino) phenylacetamido] penicillanic acid, m.p. 150—153°C (decomp.), yield 73%.	5 °
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1780 (lactam), 1740 (ester), 1710—1680 (—CON<) NMR (CDCl ₃) τ values: 2.55 (5H), 4.3—4.55 (3H), 5.6 (1H), 5.7 (3H), 6.0 (2H), 6.3 (2H), 7.4 (2H), 7.5 (4H), 8.5 (6H)	2
10	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a β -morpholinoethyl ester of 6-[D(-)- α -(4-n-octyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 103—105°C (decomp.), yield 70%.	10
15	Example 19. (1) To a solution of 8.7 g of a sodium salt of D(-)-\alpha-phenylglycine in 50 ml of water were added 50 ml of ethyl acetate and 5.05 g of triethylamine. To the resulting mixture was gradually added 9.5 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride at 0° to 5°C over a period of 15 minutes, and then the mixture was reacted at 5° to	15
20	15°C for 30 minutes. After the reaction, the aqueous layer was separated off, washed with diethyl ether, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and dried to obtain 14.1 g of $D(-)$ - α -(4-methyl-2,3-dioxo-1-piperazinocarbonyl-amino)phenylacetic acid, m.p. 138—141°C (decomp.), yield 87%. Recrystallization	20
25	from hydrous butanol gave white crystals, m.p. 140—142°C (decomp.).	25
	Elementary analysis (for $C_{14}H_{15}N_8O_5$. H_2O): Calculated (%) C: 52.01 H: 5.30 N: 13.00 Found (%) C: 52.24 H: 5.32 N: 12.87 IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1710, 1700, 1660	#
30	(2) Into a solution of 10 g of the above-mentioned $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid in 200 ml of acetone was dropped a solution of 5.2 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone with stirring to deposit crystals. The deposited crystals were collected by filtration and then washed with acetone to obtain 9.6 g of a sodium salt of $D(-)$	30
35	washed with acetone to obtain 9.6 g of a sodium salt of D(-)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 165°C (decomp.), yield 95%. (3) To a suspension of 8.8 g of the above-mentioned sodium salt of D(-)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 80 ml of methylene chloride was added 20 mg of N-methylmorpholine. Into the resulting mixture was	35
40	dropped a solution of 3.1 g of ethyl chlorocarbonate in 20 ml of methylene chloride at -20° to -15°C over a period of 5 minutes, and the mixture was reacted at said temperature for 1 hour. Into this reaction liquid was dropped a solution of 9.4 g of a triethylamine salt of 6-aminopenicillanic acid in 40 ml of methylene chloride at -40° to -30°C over a period of 10 minutes, and the resulting mixture was reacted at -40° to -20°C over a period of 1 hour. After the reaction, the temperature of the reaction	40
45	liquid was gradually elevated to 0°C over a period of 1 hour, and the mixture was then subjected to extraction with 100 ml of water. Subsequently, the aqueous layer was separated off, and the methylene chloride layer was further subjected to extraction with 50 ml of water, and the resulting aqueous layer was combined with the aforesaid aqueous	45
50	layer. The combined aqueous layer was adjusted to a pH of 2 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, dried and then dissolved in 200 ml of acetone. Into the resulting solution was dropped a solution of 4 g of a sodium salt of 2-ethylhexanoic acid in 40 ml of acetone over a period of 10 minutes to deposit crystals.	50
55	The deposited crystals were collected by filtration, washed with acetone and then dried to obtain 11.4 g of a sodium salt of $6-[D(-)-\alpha-(4-\text{methyl-}2,3-\text{dioxo-}1-\text{piperazino-} \text{carbonylamino})$ phenylacetamido] penicillanic acid, m.p. 170°C (decomp.), yield 80.8%. The above-mentioned operation was repeated, except that the $D(-)-\alpha-(4-\text{methyl-}2,3-\text{dioxo-}1-\text{piperazinocarbonylamino})$ phenylacetic acid was replaced by each of the	55
60	compounds of formula (V) shown in Table 18, to obtain respective objective compounds as shown in Table 18. The structure of each objective compound was confirmed by IR and NMR.	60

Table 18

Objective compound	$D(-)-$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $COONR$	D(-)- CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH S CH ₃ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃ CH ₂ CH ₃	D(-)-CH2 (CH2)2 CH2 - N - CONHCHCONH - S CH3 CH3 COONB
Compound of formula (V)	D(-)-	D(-)-	D(-)-
	CH ₂ CH ₂ -N N-сомненсоон	CH ₃ CH ₂ CH ₂ -N N-СОNНСНСООН	СН ₂ (СН ₂) ₂ СН ₂ -N N-соинсисоон

	Example 20.	
5	(1) To a solution of 2.28 g of $D(-)-\alpha$ -amino-1,4-cyclohexadienylacetic acid in 15 ml of N NaOH were added 20 ml of ethyl acetate and 2.1 ml of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was gradually added 1.69 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. Sub-	ء 5
J	sequently, the mixture was reacted for 30 minutes with ice-cooling, and then the aqueous layer was separated off. To the aqueous layer was further added 20 ml of ethyl acetate. The resulting mixture was adjusted to a pH of 2 by addition of 2N hydrochloric acid	•
10	with ice-cooling, and the ethyl acetate layer was separated off. The organic layer was sufficiently washed with water, dried over anhydrous magnesium sulfate, freed from the solvent by distillation under reduced pressure and then incorporated with isopropyl alcohol to deposit crystals. The deposited crystals were collected by filtration to obtain 2.5 g of white crystals of $D(-)-\alpha-(4-\text{methyl-}2,3-\text{dioxo-}1-\text{piperazinocarbonylamino})$ -	10
	1,4-cyclohexadienylacetic acid, m.p. 140-145°C (decomp.), yield 74%.	
15	IR (KBr) cm ⁻¹ : ν_{NH} 3300, $\nu_{C=0}$ 1715, 1660 NMR (d ₆ -DMSO) τ values: 0.57 (1H, d), 4.26 (1H, s), 4.36 (2H, s), 5.29 (1H, d), 6.07—6.18 (2H, m), 6.38—6.49 (2H, m), 7.05 (3H, s), 7.35 (4H, s)	15
20	(2) To a suspension of 0.45 g of the above-mentioned $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid in 15 ml of anhydrous methylene chloride was added 0.24 ml of N-methylmorpholine with stirring to form a solution. After cooling the solution of -10° C, 3 ml of an anhydrous methylene chloride solution containing 0.24 g of ethyl chlorocarbonate was dropped into the solution, and	20
25	the resulting mixture was reacted at said temperature for 90 minutes. Subsequently, the reaction liquid was cooled to -20° C, and 5 ml of a methylene chloride solution containing 0.70 g of a triethylamine salt of 6-aminopenicillanic acid and 0.31 ml of triethylamine was gradually dropped into the reaction liquid. The resulting mixture was reacted at -20° C for 1 hour, at -20° to 0° C for 1 hour, and at 0° to 5° C for 1 hour.	25
30	Thereafter, the reaction liquid was freed from the solvent by distillation under reduced pressure. The residue was dissolved in 10 ml of water and then washed with 10 ml of ethyl acetate. The aqueous layer was again incorporated with 15 ml of ethyl acetate, and then adjusted to a pH of 2.0 by addition of 2N HCl with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, dried over anhydrous	30
35	magnesium sulfate, and freed from the solvent by distillation under reduced pressure to obtain 0.74 g of white crystals of $6-[D(-)-\alpha-(4-\text{methyl-2,3-dioxo-1-piperazino-carbonylamino})-1,4-cyclohexadienylacetamido] penicillanic acid, m.p. 84—87°C (decomp.), yield 87%.$	35
40	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1780 (lactam), 1730—1660 (—COOH, —CON<) NMR (d_6 -DMSO) τ values: 0.55 (1H, d), 0.95 (1H, d), 4.22 (1H, s), 4.35 (2H, s), 4.41—4.61 (2H, s), 4.92 (1H, d), 5.75 (1H, s), 6.05 (2H, bs), 6.40 (2H, bs), 7.03 (3H, s), 7.35 (4H, s), 8.40 (3H, s), 8.52 (3H, s)	40
	The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogenearbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.	
45 .	The above-mentioned operation was repeated, except that the $D(-)$ - α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid was replaced by each of the compounds of formula (V) shown in Table 19, to obtain respective objective compounds as shown in Table 19. The structure of each objective compound was confirmed by IR and NMR.	45

Table 19

Objective compound	$D(-)- 0 0 CH_{2}CH_{2} - N N + CONHCHCONH $	$D(-)- \begin{matrix} 0 & 0 & 0 \\ CH_2 & N - CONHCHCONH \end{matrix}$ $CH_3 CH_2 CH_2 - N - CONHCHCONH \end{matrix}$ $CH_3 CH_2 CH_2 - N - CONHCHCONH \end{matrix}$	D(-)- CH ₂ (CH ₂) ₂ CH ₂ -N -CONHCHCONH S CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -N -CONHCHCONH CH ₂ COONa
Compound of formula (V)	D(-)- O O CH3CH2-N N-CONHCHCOOH	D(-)- сн ₃ сн ₂ сн ₂ -и и-соинснсоон	D(-)- CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCOOH

	Example 21.	
5	(1) To a solution of 2.2 g of DL- α -amino-2-thienylacetic acid in 14 ml of a N sodium hydroxide solution was added at 0°C 2.2 g of triethylamine. To the resulting mixture was further added 3.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride little by little at said temperature. Subsequently, the mixture was reacted at 0°C for 30 minutes, and then at room temperature for 30 minutes. After the reaction, the reaction liquid was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid to deposit	5
10	crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 3.5 g of DL-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 214—215°C (decomp.), yield 80.5%.	. 10
15	IR (KBr) cm ⁻¹ : ν _{C=0} 1710, 1680—1660 (2) Into a solution of 3.5 g of the above-mentioned DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 100 ml of acetone was dropped a solution of 1.86 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone, upon which crystals were deposited. The deposited crystals were collected by filtration and	15
15	then washed with acetone to obtain 3.5 g of a sodium salt of DL-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 175—176°C (decomp.). (3) To a suspension of 3.3 g of the above-mentioned sodium salt of DL-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 50 ml of methyl-	
20	ene chloride was added 30 mg of N-methylmorpholine, and the resulting mixture was then cooled to -20° to -15°C. Into the resulting mixture was dropped a solution of 1.3 g of ethyl chlorocarbonate in 20 ml of methylene chloride over a period of 5 minutes, and the mixture was stirred at said temperature for 90 minutes. Subsequently, a solution of 3.3 g of a triethylamine salt of 6-aminopenicillanic acid in 50 ml of methylene	20
25	chloride was dropped into the mixture at -50° to -40° C over a period of 20 minutes, and the resulting mixture was reacted with stirring at -40° to -30° C for 30 minutes, at -30° to -20° C for 30 minutes, and then at -20° to 0° C for 30 minutes. After the reaction, the solvent was removed by distillation under reduced pressure, and the	25
30	residue was dissolved in water. The resulting aqueous solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.1 g of 6-[DL-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetamido]penicillanic acid, m.p. 185°C (decomp.), yield 80.5%.	30
35	IR (Nujol Registered Trade Mark) cm ⁻¹ : $\nu_{C=0}$ 1780 (lactam), 1715 (—COOH), 1685—1675 (—CON<) NMR ((CD ₃) ₂ CO) τ values: 0.5 (1H), 1.8 (1H), 2.6 (1H), 2.85—3.05 (2H), 4.0 (1H), 4.2—4.5 (2H), 5.7 (1H), 5.8—6.0 (2H), 6.2—6.4 (2H), 6.95 (3H), 8.4 (3H), 8.45 (3H)	35
40	The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogenearbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof. The above-mentioned operation was repeated, except that the sodium salt of DL-	40
45	a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid was replaced by each of the compounds of formula (V) shown in Table 20, to obtain respective objective compounds as shown in Table 20. The structure of each objective compound was confirmed by IR and NMR.	45

Table 20

Compound of formula (V)	Objective compound
DL- OOO CH3CH2-NN-CONHCHCOONB	CH ₂ CH ₂ -N N-CONHCHCONH SCH ₂
DL- CH3CH2CH2-NN-CONHCHCOONA	DL- OH2CH2-N N-CONHCHCONH S CH3 S CH3
DL- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCOONa	DL- OCH2 CH2 CH2 CH2 N-CONHCHCONH SCH3 SCH3 SCH3

	Example 22.	
•	To a suspension of 0.9 g of 6- $[D(-)$ - α -aminophenylacetamido]penicillanic acid in 30 ml of anhydrous ethyl acetate were added at 5° to 10°C 0.55 g of triethylamine and 0.6 g of trimethylsilyl chloride. The resulting mixture was reacted at 15° to 20°C	۽
5	for 3 hours to form trimethylsilylated 6-[D()-\alpha-aminophenylacetamido]penicillanic	- 5
	acid. To this acid was then added 1 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at 15° to 20°C for 2 hours. After the reaction, a deposited triethylamine hydrochloride was separated by filtration, and the	#
	filtrate was incorporated with 0.4 g of n-butanol to deposit crystals. The deposited	
10	crystals were collected by filtration to obtain 1.25 g of white crystals of $6-[D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido] penicillanic acid. Into a solution of said crystals in 30 ml of tetrahydrofuran was dropped a solution of 0.38 g of a sodium salt of 2-ethylhexanoic acid in 10 ml of tetrahydrofuran, upon which white crystals were deposited. The deposited crystals were collected by filtration, sufficiently$	10
15	washed with tetrahydrofuran and then dried to obtain 1.25 g of a sodium salt of $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] penicillanic acid, m.p. 183—185°C (decomp.), yield 90%.$. 15
	Example 23.	
20	To a suspension of 4 g of a trihydrate of $6-[D(-)-\alpha$ -aminophenylacetamido]-penicillanic acid in 40 ml of water was added 20 ml of ethyl acetate, and the resulting mixture was cooled to 2°C. Subsequently, the mixture was incorporated with 1.37 g of potassium carbonate, and then stirred at 2° to 3°C for 2 minutes. Thereafter, 1.89 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was added to the mixture at said	20
	temperature over a period of 10 minutes, and the resulting mixture was reacted at said	٠.
25	temperature for 15 minutes. After the reaction, slight amounts of insolubles were separated by filtration, and the filtrate was charged into 80 ml of ethyl acetate. Into the	25
	resulting mixture was dropped 5 ml of 2N HCl at 20° to 22°C over a period of 5 minutes, and the mixture was stirred at said temperature for 5 hours to deposit crystals.	•
20	The deposited crystals were collected by filtration, washed two times with 4 ml of water, further washed two times with 4 ml of isopropanol, and then dried to obtain 4.0 g of a	30
30	dihydrate of $6-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido]penicillanic acid, m.p. 156—157°C (decomp.), yield 75.4%.	
	IR (KBr) cm ⁻¹ : v _{C=0} 1775, 1740, 1695, 1670	
35	NMR (d _s -DMSO) τ values: 0.18 (1H, d), 0.77 (1H, d), 2.66 (5H, s), 4.30 (1H, d), 4.40 (3H, br), 4.48 (1H, g), 4.65 (1H, d), 5.80 (1H, s), 6.12 (2H, bs), 6.45 (2H, bs), 7.06 (3H, s), 8.48 (3H, s), 8.60 (3H, s)	35
	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-	
	1-piperazinocarbonyl chloride was replaced by 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a monohydrate of $6-[D(-)-\alpha-(4-\text{ethyl-2},3-\text{dioxo-1-piperazino-carbonylamino})$ phenylacetamido] penicillanic acid, m.p. 154—156°C (decomp.), yield	40
40	carbonylamino)phenylacetamido]penicillanic acid, m.p. 154—156°C (decomp.), yield 84.8%.	40
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1775, 1735, 1705, 1680, 1665	
	NMR (d ₀ -DMSO) τ values: 0.20 (1H, d), 0.76 (1H, d), 2.69 (5H, s), 4.32 (1H, d), 4.53 (1H, q), 4.64 (1H, d), 5.00 (3H, br), 5.83 (1H, s), 6.13	
45	(2H, bs), 6.49 (2H, bs), 6.62 (2H, q), 8.44 (3H, s), 8.58 (3H, s), 8.91 (3H, t)	. 45
	The thus obtained monohydrate was neutralized with an aqueous sodium hydrogen-	=
	carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of $6-[D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido]-	50
50	Further, a solution in 10 ml of nitromethane of 2 g of the aforesaid dihydrate of	JU ,
	6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid was allowed to stand overnight to deposit crystals, which were$	
55	then collected by filtration to obtain 2 g of a monohydrate of a nitromethane addition product of $6-[D(-)-\alpha-(4-\text{methyl-}2,3-\text{diox}o-1-\text{piperazinocarbonylamino})$ phenylacet-	55
	amido] penicillanic acid, m.p. 128—130°C (decomp.), yield 92.2%.	
	Flomentary analysis (for C. H. N.O.S. CH.NO. H.O.)	

Elementary analysis (for C₂₂H₂₃N₃O₇S . CH₃NO₂ . H₂O): Calculated (%) C: 47.42 H: 5.19 N: 14.43 Found (%) C: 47.94 H: 5.13 N: 14.53

	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1770, 1735, 1700, 1680	
<u>.</u>	NMR (d ₀ -DMSO) τ values: 0.22 (1H, d), 0.80 (1H, d), 2.69 (5H, s), 3.30 (3H, br), 4.30 (1H, d), 4.46—4.70 (2H), 5.67 (3H, s), 5.81 (1H, s),	
•	6.13 (2H, bs), 6.46 (2H, bs), 7.07 (3H, s), 8.45 (3H, s), 8.58 (3H, s)	
. 5	Example 24. To a suspension of 1.6 g of a trihydrate of D(-)-\alpha-aminobenzyl penicillin in 20 ml of water was added at 2° to 3°C 0.54 g of potassium carbonate, and the resulting mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4-	5
10	ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl	10
15	at 15° to 20°C over a period of 2 minutes, and the mixture was stirred at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152-154°C	15
20	(decomp.), yield 80.2%. The thus obtained product was neutralized with an aqueous sodium hydrogen-carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product.	20
	Example 25.	
25	A suspension of 4.0 g of a monohydrate of 7- $[D(-)-\alpha$ -aminophenylacetamido]-3-methyl- Δ^3 -cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was	. 25
30	maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to	30
35	5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - \text{methyl} - 3 - \text{cephem} - 4 - \text{carboxylic acid, m.p. } 185-186°C (decomp.), yield 86%.$	35
40	IR (KBr) cm ⁻¹ : $v_{C=0}$ 1770—1760 (lactam), 1720—1660 (—CON<, —COOH) NMR (d_0 -DMSO) τ -values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s)	40
45	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each chiesting compound was confirmed by IP.	45

as shown in Table and NMR.

Table 21

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-
CH ₃ CH ₂ -N N-COC1	CH ₂ OH ₂ -N N-CONHOHCONH - S
	m.p. (decomp.) 168°C, yield 80 %
	D(-)-
CH3CH2CH2-N N-COC1	CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH S CH ₃
-	m.p. (decomp.) 160°C, yield 80.5 %
O, O'	
CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	CH3 (CH2) 2 CH2 - N N - CONHCHCONH THO CH3
	m.p. (decomp.) 150°C, yield 76 %

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Example 26.

(1) To a solution of 0.92 g of 1-n-pentyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added 1.1 ml of triethylamine and 1.08 g of trimethylsilyl chloride. The resulting mixture was stirred at room temperature for 20 hours to form triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into a solution of 0.6 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and then at room temperature for 2 hours. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 1.21 g of pale yellow, oily 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride.

IR (film) cm⁻¹: v₀₌₀ 1790, 1720—1665

(2) A suspension of 1.70 g of a monohydrate of 7-[D(-)- α -aminophenylacetamido]-3-methyl-\(^3\)-cephem-4-carboxylic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 7 ml of an anhydrous tetrahydrofuran solution containing 1.21 g of the 4-n-pentyl-2,3-dioxo-1piperazinocarbonyl chloride obtained in (1) was dropped into the solution. During this period, the pH of the solution was maintained at a pH of 7.5 to 8.0 by addition of triethylamine. Subsequently, the resulting mixed solution was reacted at 0° to 5°C for 1 hour and then at 5° to 10°C for 2 hours while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. The aqueous layer was again charged with 40 ml of ethyl acetate, and then adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, and then dried over anhydrous magnesium sulfate. Thereafter, 10 ml of an ethyl acetate solution containing 0.75 g of sodium 2-ethylhexanoate was dropped into the layer at 0° to 5°C to deposit white crystals. The deposited crystals were collected by filtration, and washed with ethyl acetate and then with diethyl ether to obtain 1.95 g of a sodium salt of $7 - [D(-) - \alpha - (4 - n - pentyl - 2,3 - dioxo - 1 - piper-azinocarbonylamino) phenylacetamido] - 3 - methyl - <math>\Delta^3$ - cephem - 4 - carboxylic acid, m.p. 164—166°C (decomp.), yield 75%.

IR (KBr) cm⁻¹: $\nu_{C=0}$ 1750 (lactam), 1720—1660 (—CON<), 1590 (—COO^{\ominus}) NMR (d₈-DMSO|+D₂O) τ values: 2.58 (5H, s), 4.33 (1H, s), 4.49 (1H, d), 5.17 (1H, d), 6.10 (2H, bs), 6.42—6.87 (6H, m), 8.09 (3H, s), 8.60—8.90 (6H, bs), 9.12 (3H, t)

The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 22, to obtain respective objective compounds as shown in Table 22. The structure of each objective compound was confirmed by IR and NMR.

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Table 22

Objective compound	$D(-) CH_{2}(CH_{2})_{4}CH_{2}-N$ $CH_{3}(CH_{2})_{4}CH_{2}-N$ CH_{3} $CH_{3}(CH_{2})_{4}CH_{2}-N$	D(-)- CH ₂ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH CH ₄ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH CH ₄ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH CH ₄ (CH ₂) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₂) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₂) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH ₄ (CH ₄) ₅ CH ₄ -N N-CONHCHCONH CH	D(-)- $CH_{2}(CH_{2})_{6}CH_{2}-M \qquad CONHCHCONH \qquad S$ $CH_{3}(CH_{2})_{6}CH_{2}-M \qquad CONHCHCONH \qquad S$ $CH_{3}(CH_{2})_{6}CH_{2}-M \qquad CH_{3}$ $M.p. (decomp.) 154°C, yield 78 %$
Reactive derivative of compound of formula (III)	одо сн ₃ (сн ₂)4сн ₂ -и м-сос1	он ₃ (сн ₂) ₅ сн ₂ -м м-сос1	одо сн ₃ (сн ₂) ₆ сн ₂ -м м-сос1

Table 22 (Cont'd)

сн ₃ сн ₂ осо-м м-сост	D(-)- CH ₃ CH ₂ OCO-N N-CONHCHCONH S CH ₃ CH ₃ CH ₂ OCO-N N-CONHCHCONH CH ₃ COONA m.p. (decomp.) 185 - 188°C, yield 77 %
сн ₃ (сн ₂) ₄ сн ₂ -м м-сос1	D(-)- CH ₂ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH CH ₃ COON m.p. (decomp.) 135 - 137°C, yield 79.2 %

5	Example 27. Using 1.5 g of a hydrochloride of methoxymethyl ester of $7-[D(-)-\alpha-amino-phenylacetamido]-3-methyl-\Delta^3-cephem-4-carboxylic acid and 0.65 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 25 was repeated to obtain 1.6 g of a methoxymethyl ester of 7-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]-3-methyl-\Delta^3-cephem-4-carboxylic acid, m.p. 146—148°C (decomp.), yield 86%.$	5
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1770 (lactam), 1710 (ester), 1680—1600 (—CON<)	
10	Example 28. To a suspension of 0.20 g of $7-[D(-)-\alpha$ -aminophenylacetamido]-3-acetoxymethyl- Δ^0 -cephem-4-carboxylic acid in 15 ml of anhydrous chloroform was added 0.17 ml of triethylamine with stirring to form a solution, which was then cooled to 0° C.	10
15	To this solution was added 0.11 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at room temperature for 2 hours. After the reaction, the reaction liquid was evaporated under reduced pressure, and the residue was dissolved in 15 ml of water. The resulting solution was washed with 10 ml of ethyl acetate. The aqueous layer was again charged with 20 ml of ethyl acetate, and then	15
20	adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, successively washed with water and a saturated aqueous sodium chloride solution, and then dried over magnesium sulfate. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 0.22 g of white crystals of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piper-azinocarbonylamino}) phenylacetamido] - 3 - acetoxymethyl - \Delta^3 - cephem - 4 - carboxylic acid, m.p. 175°C (decomp.), yield 76%.$	20
25	IR (KBr) cm ⁻¹ : $\nu_{G=0}$ 1770 (lactam), 1720—1650 (—CON<, —COOH) NMR (d _e -DMSO) τ values: 0.23 (1H, d), 0.63 (1H, d), 2.66 (5H, s), 4.32 (1H, q), 4.43 (1H, d), 5.05 (1H, d), 5.21 (2H, q), 6.15 (2H, bs), 6.40 (2H, bs), 6.57 (2H, bs), 7.0 (3H, s), 8.0 (3H, s)	25
30	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 23, to obtain respective objective compounds as shown in Table 23. The structure of each objective compound was confirmed by IR and NMR.	30

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Objective compound	$D(-)- \begin{matrix} 0 & 0 & 0 \\ \text{CH}_3\text{CH}_2\text{CH}_2 - \text{N} & \text{N-CONHCHCONH} \\ \hline $	$D(-) CH_3CH_2-N$ $M-CONHCHCONH$ CH_2OCOCH_3 CH_2OCOCH_3 CH_2OCOCH_3 CH_2OCOCH_3 CH_2OCOCH_3 CH_2OCOCH_3 CH_2OCOCH_3	$D(-)- 0 0 0 $ $(CH3)2CH-N N-CONHCHCONH S CH2OCOCH3$ $\bigcirc 0 0 COOH$ m.p. (decomp.) 146°C, yield 82 %
Reactive derivative of compound of formula (III)	сн ₃ сн ₂ -и м-сост	сн ₃ сн ₂ -м м-сост	сн ₃) ₂ сн-м-сост

cont'd

Table 23 (Cont'd)

CH3CH2-N-CSC1	CH ₂ CH ₂ -N N-CSNHCHCONH S CH ₂ OCOCH ₃
	m.p. (decomp.) 112°C, yield 95 %
	D(-)- O O
O O O O O O	CH3-N N-CSNHCHCONH TN CH-CCH-CCH-
	COO 1000
	m.p. (decomp.) 134°C, yield 90.2 %

The aforesaid 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^8 - cephem - 4 - carboxylic acid, m.p. 175° C (decomp.), was recrystallized from hydrous acetone to obtain white crystals showing a melting point of 198° to 200°C (decomp.).

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(1) To a solution of 28.2 g of a sodium salt of D(—)-phenylglycine in 150 ml of water were added 200 ml of ethyl acetate and 18.2 g of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was added 34.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 15 minutes, and the mixture was reacted at 5° to 10°C for 15 minutes. Thereafter, the aqueous layer was separated off and adjusted to a pH of 0.5 by addition of 2N hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration and then dried to obtain 42 g of white crystals of D(—)-x-(4-methyl-2,3-dioxo-1-piperazinocarbonyl-amino) phenylacetic acid.

(2) To a suspension in 15 ml of anhydrous methylene chloride of 0.31 g of the D(—) and the collected of the obtain the obtain of the obtain d the ob

(2) To a suspension in 15 ml of anhydrous methylene chloride of 0.31 g of the D(-)-a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid obtained in the above-mentioned item (1) was added 0.11 g of N-methylmorpholine with stirring to form a solution, which was then cooled to -20°C. To this solution was added 3 ml of an anhydrous methylene chloride solution containing 0.13 g of ethyl chlorocarbonate, and the resulting mixture was reacted at -10°C to -20°C for 60 minutes

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5	to form a mixed acid anhydride. Into the thus formed acid anhydride was dropped a solution formed by adding 0.50 ml of triethylamine to a suspension in 5 ml of methanol of 0.41 g of 7 - amino - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid. After the dropping, the resulting mixture was reacted at -50° to -30°C for 30 minutes, at -30° to -20°C for 30 minutes, at -20° to	5
	0°C for 60 minutes, and then at room temperature for 30 minutes. Thereafter, the reaction liquid was concentrated under reduced pressure, and the concentrate was dissolved in 10 ml of water, washed with 5 ml of ethyl acetate, again charged with 15 ml of ethyl	
10	acetate, and then adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, insolubles were separated by filtration, and the ethyl acetate layer was separated off, successively washed with water and a saturated sodium chloride solution, dried over magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to obtain 0.58 g of pale yellow crystals of 7 - [D(-)-	10
15	α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2-(5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 160°C (decomp.), yield 91%.	15
20	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1780 (lactam), 1650—1720 (—CON<, —COOH) NMR (d ₀ -DMSO) τ values: 0.2 (1H, d), 0.6 (1H, d), 2.60 (5H, s), 4.35 (1H, q), 4.40 (1H, d), 5.0 (1H, d), 5.70 (2H, q), 6.10 (2H, bs), 6.25—6.55 (2H, 2H, bs), 7.0 (3H, s), 7.30 (3H, s)	20
	The above-mentioned operation was repeated, except that the $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 24, to obtain respective objective compounds as shown in Table 24. The structure of each objective compound was confirmed	,
25	by IR and NMR.	25

Table 24

Compound of formula (V)	Objective compound
D(-)- 0 0 сн ₃ сн ₂ -и м-сомнснсоон	D(-)- 0 0 CH3CH2-N N-CONHCHCONH S CH2S N-N CH2S CH2 CH2S CH2 CH2S CH2 CH2S CH2 CH2S CH2 CH2S CH2
D(-)- CH ₂ CH ₂ CH ₂ -м м-сомнснсоон	D(-)- CH ₃ CH ₂ CH ₂ -N CH ₃ CH ₂ -N CH ₃ CH ₂ -N CH ₃ CH ₂ S CH ₃ CH ₃ CH ₂ S CH ₃ CH ₃ CH ₂ S COOH m.p. (decomp.) 147°C, yield 85.4 %
D(-)- CH ₂ (CH ₂) ₂ CH ₂ -и и-соинсисоон	D(-)- CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH S O CH ₂ S S N-N (O) O COOH m.p. (decomp.) 144 ^O C, yield 84.3 %

Table 24 (Cont'd)

D(-)-	1-CONHCHCOOH	m.p. (decomp.) 167°C, yield 93 %
D(-)-	O M N-connected)

2 15 The above-mentioned operation was repeated, except that the $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 25, to obtain respective objective compounds as shown in Table 25. The structure of each objective compound was confirmed by IR and NMR. Using 0.3 g of D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.33 g of 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4-terrazolyl) - thiomethyl] - Λ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, to obtain 0.5 g of 7 - [D(-) - α - (4 - methyl 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl 1,2,3,4 - tetrazolyl) - thiomethyl] - Λ^3 - cephem - 4 - carboxylic acid, m.p. 161—163°C (decomp.), yield 76%. IR (nujol) cm⁻¹: v₀₌₀ 1775 (lactam), 1720—1660 (—CON<, —COOH)
NMR (d₆-DMSO) τ values: 0.02 (1H, d), 0.34 (1H, d), 2.48 (5H, s), 4.17
(1H, q), 4.26 (1H, d), 4.92 (1H, d), 5.66 (2H, s), 6.01 (5H, s), 6.35 (4H, s), 7.0 (3H, s) 15 10

Table 25

Compound of formula (V)	Objective compound
D(-)- 0 0	ρ(-)-
CH ₂ CH ₂ -N N-CONHCHCOOH	CH ₂ CH ₂ -N N-CONHOHCONH N CH ₂ S N-N
(h) (h)	* * CH3 COOH THE CH3 m.p. (decomp.) 170°C, yield 63.6 %
D(-)-	D(-)-
CH3-N N-CONHCHCOOH	CH3-N N-CONHCHCONH S N-N
)	m.p. (decomp.) 173°C, yield 68 % CH ₃
D(-)- 0 0	D(-)-
О п п п п п п п п п п п п п п п п п п п	O N N-CONHCHCONE S N-N
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Anhydrous methylene chloride was substituted for the methanol used in Example 29.

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Using 0.30 g of D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.34 g of 7 - amino - 3 - [5 - (1,3,4 - thiadiazolyl)-thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, to obtain 0.47 g of 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 158—159°C (decomp.), yield

IR (nujol) cm⁻¹: $\nu_{0=0}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the D(-) - α -(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid was replaced by D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid, to obtain 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl]- Δ^3 - cephem - 4 - carboxylic acid, m.p. 123°C (decomp.), yield 64.5%. 10 15

Example 32.

Using 0.31 g of D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.39 g of 7 - amino - 3 - [2 - (1 - methyl - 1,3,4-triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, except that the methanol was replaced by anhydrous methylene chloride, to obtain 0.43 g of 7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^a - cephem - 4 - carboxylic acid, yield 70%.

IR (Nujol) cm⁻¹: $\nu_{C=0}$ 1780 (lactam), 1720—1650 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 26, to obtain respective objective compounds as shown in Table 26. The structure of each objective compound was confirmed by IR and NMR.

Table 26

Compound of formula (V)	Objective compound
D(-)-	D(-)-
CH ₂ CH ₂ -N -CONHCHCOOH	CH ₂ CH ₂ -N N-CONHCHCONH S CH ₂ S N N CH ₂ S N N CH ₂ S N N N CH ₂ S N N N CH ₂ S N N N N N N N N N N N N N N N N N N N
<u></u>	m.p. (decomp.) 147^{0} C, yield 68.5%
D(-)-	D(-)a
O N N-CONHCHCOOH	O N N-CONHORICONH S CH2S IN
(i)	CUOH CH ₂ m.p. (decomp.) 158 ⁰ C, yield 74.5 %

Example 33.

The procedure of Example 29 was repeated, except that the D(-)-a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 27, to obtain respective objective compounds shown in Table 27. The structure of each objective compound was confirmed by IR and NMR.

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Compound of formula (V)	Objective compound
D(-)-	D(-)-
сн ₃ со-и м-сомеснсоон	CH ₃ CO-N N-CONHCHCONH S N-N CH ₂ CH ₃ CH ₃ CH ₃ COOH
D(-)-	D(-)-
CH ₃ SO ₂ -N N -CONHÇHCOOH	CH ₂ SO ₂ -N N-CONHCHCONH S N-N CH ₂ S S CH ₃
D(-)-	D(-)-
сн ₃ -и м-сомнсисоон	CH ₃ -N N-CONHCHCONH S N-N CH ₂ S L _S L _{CH₃}

Table 27 (Cont'd)

D(-)-	D(-)-
сн ₃ сн ₂ -и м-сомнснсоон	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S S N-N CH ₃ CH ₂ S S S N-N CH ₃
D(-)- СН ₃ CONHCO-и и-СОNHCHCOOH	D(-)- CH ₂ CONHCO-N N-CONHCHCONH S CH ₂ S-L CH ₃ COOH
D(-)- CH3-N N-CONHCHCOOH	D(-)- CH3-N N-CONHCHCONH S N-N CH2S-US US CH3

cont'd -

Table 27 (Cont'd)

D(-)~	D(-)-
CH ₂ CH ₂ -N N-CONHCHCOOH	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S L CH ₃ CH ₃ CH ₂ S L CH ₃
D(-)-	D(-)-
ну м-сомненсоон	HN N-CONHCHCONH S N-N IN CH2S LS LCH3
D(-)-	D(-)-
CH ₂ CO-N N-CONHCHCOOH	CH ₂ CO-N N-CONHCHCONH S N-N CH ₂ CH ₃

Example 34.

The procedure of Example 30 was repeated, except that the D(—)-\(\pi\)-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 28, to obtain respective objective compounds shown in Table 28. The structure of each objective compound was confirmed by IR and NMR.

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Compound of formula (V) $D(-)$ - $D(-)$ - $CH_{3}CO-1$ O - $CH_{3}C$		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Compound of formula (V)	Objective compound
$^{\circ}$ Соинсисоон $^{\circ}$ Си $^{\circ}$ Соинсисоин $^{\circ}$ Соон $^{\circ}$ Соинсисоин $^{\circ}$ Соон $^{\circ}$ Соинсисоон $^{\circ}$ Соинсисоон $^{\circ}$ Соинсисоон $^{\circ}$ Соинсисоон $^{\circ}$ Си $^{\circ}$ Соинсисоон $^{\circ}$ Си $^{\circ}$ Соон $^{\circ}$ Си $^{\circ}$ Си $^{\circ}$ Соон $^{\circ}$ Си	D(-)-	D(-)-
D(-)- CH ₂ SO ₂ -N N-CONHCHCONH S N- CH ₃ SO ₂ -N N-CONHCHCONH S N- CH ₃ -N N-CONHCHCONH S N- D(-)- CH ₃ -N N-CONHCHCONH S N- CH ₃ -N N-CONHCHCONH S N- CH ₃ -N N- CH	сн ₅ со-м м-сомненесоон	COOH
CH3 SO2-N N-CONHCHCOOH D(-)- D(-)- CH3 SO2-N N-CONHCHCONH D(-)- CH3 SO2-N N-CONHCHCONH CH2 S O2-N N-CH2 S N-N CH3 N-CONHCHCOOH CH3 CH3 N-CONHCHCONH CH3 N-CONHCHCOOH CH3 CH3 N-CONHCHCONH CH4 CH3 N-CONHCHCONH CH4 CH3 N-CONHCHCONH CH5 CH4 CH5 N-CONHCHCONH CH5 CH4 CH5 N-CONHCHCONH CH5 CH5 CH5 N-CONHCHCONH CH5 CH5 CH5 N-CONHCHCONH CH6 CH5 CH5 N-CONHCHCONH CH7 CH7 CH5 N-CONHCHCONH CH7 CH5 N-CONHCHCONH CH7 CH7 CH5 N-CONHCHCONH CH7	D(-)-	D(-)-
D(-)- OCH-CONHCHCOOH CH-2-N N-CONHCHCONH SOOH CH-2-N N-CONHCHCONH CH-2-N N-CH-2-S N CH-3-N N-CONHCHCONH CH-3-N N-CH-2-S N CH-3-N N-CONHCHCONH OCH-3-N N-CH-2-S N OCH-3-N N-CH-3-S N OCH-3-N N	CH ₂ SO ₂ -N N-conhchcooh	COOH
CH ₂ -N N-CONHCHCONH S N CH ₂ S N	D(-)-	D(-)-
	CH3-N N-CONHCHCOOH	S CH2S L

Table 28 (Cont'd)

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D(-)-	D(-)-
сн ₃ сн ₂ -и и сомненесоон	CH ₂ CH ₂ -N N-CONHCHCONH S N-N O CH ₂ CH ₂ S N-N CH ₂ CH ₂ S N-N CH ₃ CH ₂ S CH ₃ S CH ₃ S
D(-)-	D(-)-
сн ₃ соинсо-и л-соинснсоон	CH ₂ CONHCO-N N-CONHCHCONH S N-N N-N N-N N-N N-N N-N N-N N-N N-N N
D(-)-	D(-)-
снз-и м-сомнснсоон	CH ₂ -N N-CONHCHCONH S N-N CH ₂ S UN N CH ₂ S UN N CH ₂ S UN N CH ₃

Table 28 (Cont'd)

D(-)-	D(-)-
сн ₃ сн2-м м-сомнснсоон	CH ₂ CH ₂ -N N-CONHCHCONH S OF CH ₂ S N-N CH
D(-)- о ни у-сомнеснесоон о	D(-)- O
D(-)- сн ₃ со-и и-соинснсоон	D(-)-CONHCHCONH - S - N - N - N - N - CH2CO-N - N - N - CH2CO-N - N - N - CH2CO-N - N - N - N - N - N - N - N - N - N

147	1,508,062	147
5	Example 35. (1) To a suspension of 0.9 g of $D(-)$ - α -alanine in 15 ml of water was added 2.05 g of triethylamine to dissolve $D(-)$ - α -alanine in water, and the resulting solution was cooled to 0°C. To the solution was added 2.3 g of 4-methyl-2,3-dioxo-1-piperazino-carbonyl chloride over 15 minutes, after which reaction was effected for 30 minutes with ice-cooling. Dilute hydrochloric acid was then added to the reaction product to adjust the pH thereof to 2.0. The water was removed by distillation under reduced pressure. and 30 ml of acetone was added to the residue, after which insolubles were filtered off. To the resulting acetone solution was added 10 ml of an acetone solution of 1.6 g of a sodium salt of 2-ethylhexanoic acid, and the deposited crystals were collected by filtration, and dried to obtain 2.1 g of a sodium salt of $D(-)$ - α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)propionic acid having a melting point of 115—8°C (decomp), yield 78.5%.	5
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1700, 1680, 1600 (—CON<, —COO [©])	
15	(2) In the same manner as in Example 32, $7 - [D(-) - \alpha - (4 - \text{methyl-} 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] -3 - acetoxymethyl - Δ^3 -cephem - 4 - carboxylic acid was obtained from a sodium salt of $D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ propionic acid and 7 - amino - 3-	15
20	acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid. The thus obtained product was dissolved in 20 ml of acetone, and a solution of 0.65 g of a sodium salt of 2-ethylhexanoic acid in 5 ml of acetone was added to the resulting solution. The deposited crystals were collected by filtration and dried to obtain 1.2 g of sodium salt of 7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - \text{piperazinocarbonylamino})$ propionamido] - 3 - acetoxy-	20
25	methyl - Δ^3 - cephem - 4 - carboxylic acid having a melting point of 195°C (decomp.), yield 67.7%.	25
• .	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1780 (lactam), 1710—1660 (—CON<), 1600 (—COO \ominus)	
30	Example 36. In the same manner as in Example 32, $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p - hydroxyphenylacetamido] - 3 - [5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid was obtained from 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4 - \tetrazolyl) - \text{thiomethyl}] - \Delta^3 - cephem - 4 - carboxylic acid and D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p - hydroxyphenylacetic acid. Melting point (decomp.), 147—9°C; yield, 62.0%.$	30
35	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1765 (lactam), 1720—1660 (—CON<, —COOH)	35
40	Example 37. In the same manner as in Example 29, $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] -3 - azidomethyl - Δ^3 - cephem-4 - carboxylic acid was obtained from $D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid and 7 - amino - 3 - azidomethyl - Δ^3 -cephem - 4 - carboxylic acid. Melting point (decomp.), 185 — 8° C; yield, 68.0% .	40
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1775 (lactam), 1720—1660 (—CON<, —COOH) ν_{N_3} 2090	45
- 45 -	Example 38. In 10 ml of a phosphoric acid buffer solution of a pH of 6.3 was suspended 0.57 g of $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - acetoxymethyl - \Delta^3 - cephem - 4 - carboxylic acid, and 0.07 g of sodium hydrogencarbonate was dissolved therein. To the solution was then added 0.12 g$	45
50	of 1-methyl-5-mercapto-1,2,3,4-tetrazole to dissolve the latter in the former, and the solution was subjected to reaction for 24 hours while maintaining the pH of the solution at 6.5—6.7 by using dilute hydrochloric acid and sodium hydrogencarbonate. After the reaction, the reaction liquid was cooled, and then adjusted to a pH of 5.0 by adding dilute hydrochloric acid. The reaction liquid was sufficiently washed with ethyl acetate,	50
55	after which the aqueous layer was separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid thereto. The deposited crystals were collected by filtration and dried after which the dried crystals were weshed with ethal actain to obtain	55

tion and dried, after which the dried crystals were washed with ethyl acetate to obtain 0.40 g of $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$

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phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 -cephem - 4 - carboxylic acid, m.p. 163—165°C (decomp.), yield 74.5%.

IR (KBr) cm⁻¹: $\nu_{\rm C=0}$ 1775 (lactam), 1720—1660 (—CON<, —COOH) NMR (d_e-DMSO) τ values: 0.18 (1H, d), 0.55 (1H, d), 2.64 (5H, s), 4.3 (1H, q), 4.4 (1H, d), 5.0 (1H, d), 5.75 (2H, s), 6.05 (5H, s), 6.3—6.8 (6H), 8.92 (3H, t)

In the same manner as above, the objective compounds shown in Table 29 were obtained from 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or 7- [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and the compounds of formula (VII) shown in Table 29. All the objective compounds were D(-) isomers, and the structure of each objective compound was confirmed by IR and NMR.

Table 29

Compound of formula (VIII) N-N SH CH3 SH CH3 SH
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cont'd

Table 29 (Cont'd)

CH ₃ -N N-CONHCHCONH S CH ₂ S N-N (O) 0 COOH H CH ₂ S N-N (O) 0 COOH H CH ₂ S N-N (O) 0 COOH H CH ₂ S N-N (O) 0 COOH (O) 175 - 180°C, yield 73.4 %	CH3-N-CONHCHCONH S N-N CH3-N-CONHCHCONH S O COOH H m.p. (decomp.) 163 - 165°C, yield 72.5 %	CH ₂ CH ₂ -N N-CONHCHCONH S CH ₂ S N-N N CH ₂ S N N N N N N N N N N N N N N N N N N N
HS N H	N N N N N N N N N N N N N N N N N N N	N—N H N—N H H

cont'a -

Table 29 (Cont'd)

Table 29 (Cont'd)

CH ₂ -n n-connchconn s CH ₂ S N CH ₃ O COOH m.p. (decomp.) 156 - 157°C, yield 67.0 %	CH ₃ CH ₂ -N N-CONHCHCONH S CH ₂ S O CH ₂ S O CH ₃ CH ₂ S O COOH O CH ₃ CH ₂ S O COOH O CH ₃ CH ₂ S O CH ₃ CH ₃ S O CH ₃ CH ₃ S O CH ₃	CH3-N N-CONHCHCONH S CH2S N CH2S S COOH CHOCOMP.) 180 - 182°C, yield 68.7 %
CH ₃ SH	W → O	HS NH S

Table 29 (Cont'd)

CH ₂	CH ₃ -N N-CONHCHCONH S CH ₂ S N N N CH ₂ S N N N N N N N N N N N N N N N N N N N
HS $\left\langle \begin{array}{c} N \\ \bigcirc \end{array} \right\rangle$	CH ₃ -N N-CONFCHCONH S CH ₂ S N CH ₂ S
HS -{O}- EHO	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ CH ₂ CH ₂ CH ₂ COH m.p. (decomp.) 175 - 178°C, yield 63.0 %

Table 29 (Cont'd)

NaN ₂ CH ₂ -N N-CONHCHCONH S CH ₂ N ₃ O O O COOH O
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Table 29 (Cont'd)

S HNOCHCHNOC N N-2HO)	m.p. (decomp.) 181 - 183°C, yield 64.3 %
	CH ₂ CH ₂ OC-SNa	۵

dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^{0} -cephem - 4 - carboxylic acid, and 0.17 g of sodium hydrogencarbonate was then dissolved therein, after which 0.48 g of pyridine and 4.1 g of potassium thiocyanate were added thereto. The resulting mixture was subjected to reaction at 60°C for 5 hours while maintaining the pH of the mixture at 6.0 to 6.5 by adding dilute hydrochloric aqueous layer was then separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid. The deposited crystals were collected by filtration, dried, and then acid or sodium hydrogencarbonate. After the reaction, 20 ml of water was added to dilute the reaction mixture, which was then sufficiently washed with chloroform. The $D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - pyridinomethyl - Δ^6 - cephem - 4 - carboxylic acid betaine having a melting point washed with acetone to obtain 1.04 g (yield, 79.6%) of a thiocyanic acid salt of (<u>-</u>)<u>(</u>)

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IR (KBr) cm⁻¹: v₀₋₀ 1780 (lactam), 1720—1660 (—CON<) vSCN 2040

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In the same manner as above, a thiocyanic acid salt of $7 - [D(-) - \alpha - (4-)]$ methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine was obtained from 7 - [D(-)- α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3acetoxymethyl - A³ - cephem - 4 - carboxylic acid and pyridine, said product having the formula,

Melting point (decomp.), 180-185°C; yield, 82.0%.

In a conventional manner, the above two products were treated with an ion exchange resin to obtain the desired $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] - 3 - pyridinomethyl - <math>\Delta^3$ - cephem - 4-carboxylic acid betaine and $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] - 3 - pyridinomethyl - <math>\Delta^3$ - cephem - 4 - carboxylic acid betains boxylic acid betaine.

Example 40.

In 85 ml of anhydrous methanol was dissolved 1.5 g of a sodium salt of 7- $[D(-)-\alpha-(4-\text{ethyl}-2,3-\text{dioxo}-1-\text{piperazinocarbonylamino})$ phenylacetamido]-3- [2-(pyridyl-1-oxide)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid. To the resulting solution was added 0.65 g of anhydrous cupric chloride, and the resulting mixture was stirred at room temperature for 15 minutes and then subjected to reaction at 50°C for 14 hours. After the reaction, hydrogen sulfide gas was passed through the reaction solution with ice-cooling for 20 minutes. The resulting insolubles were filtered off, and the filtrate was concentrated under reduced pressure. To the residue was added 20 ml of a 5% aqueous sodium hydrogencarbonate solution, and the insolubles were filtered off, after which dilute hydrochloric acid was added to the filtrate to adjust the pH to 6.5. The filtrate was then washed with 10-ml portions of ethyl acetate three times, after which the aqueous layer was separated off and then adjusted to a pH of 1.8 by adding dilute hydrochloric acid thereto. The thus deposited crystals were collected by filtration and then dried under reduced pressure and washed with 20 ml of an ethyl acetate-chloroform mixed solvent (1:1 by volume) to obtain 0.40 g of 7- $[D(-)-\alpha-(4-\text{ethyl}-2,3-\text{dioxo}-1-\text{piperazinocarbonylamino})\text{phenylacetamido}]$ 3 - methoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 162—6°C (decomp.), vield 30.5%.

IR (KBr) cm⁻¹: $\nu_{0=0}$ 1770 (lactam), 1700 (—COOH), 1666 (—CON<) NMR (d_e-DMSO) τ values: 0.13 (1H, d), 0.53 (1H, d), 2.61 (5H, s), 4.31 (1H, d), 4.41 (1H, d), 4.96 (1H, d), 5.82 (2H, s), 6.10 (2H, bs), 6.33 (2H, 2H, 2H, bs), 6.79 (3H, s), 8.89 (3H, t)

The word 'Nujol' used herein is a Registered Trade Mark.

WHAT WE CLAIM IS:-1. A compound represented by the general formula (I),

> A - N - C - NH - R - CONH (1)

wherein R represents an amino acid residue; R1 represents a hydrogen atom, an esterforming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mammalian enzymic action, a silicon-phosphorus- or tin-containing group which is capable of being easily removed by treatment with H₂O or an alcohol, or a conven-

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tional salt-forming cation; n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair of R² and R³ in linked to the same carbon atom, and m pairs of R² and R³, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R² and R³ together with a common carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxyalkyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, carbamoyl, thiocarbamoyl, acylcarbamoyl, acylthiocarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylcarbamoyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y represents an oxygen or sulfur atom, and

where R² represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, amidinothio or heterocyclylthio group.

2. A compound according to claim 1, wherein R is a group represented by the formula,

wherein R⁵ represents a substituted or unsubstituted alkyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, aralkyl, aryloxy, alkylthioalkyl, or heterocyclic group; and R⁶ represents a hydrogen atom; or R⁵ and R⁶ together with a common carbon atom may form a cycloalkyl, cycloalkenyl or cycloalkadienyl ring.

3. A compound according to any one of claims 1 and 2, wherein

4. A compound according to any one of claims 1 and 2, wherein

where R⁴ is as defined in claim 1.
5. A compound represented by the general formula (Ia),

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$$A = N \longrightarrow N = CO - NH - CH - CONH \longrightarrow Z$$

$$(Ia)$$

$$(R^2 R^3)_3 \longrightarrow COOR^1$$

wherein R1, R2, R3, A and

are as defined in Claim 1 and R⁵ is as defined in Claim 2.

6. A compound represented by the general formula (Ib),

wherein R1, R2, R3, A and



are as defined in Claim 1 and R⁵ is as defined in Claim 2.

7. A compound represented by the general formula (Ic),

wherein R1, R2, R3, A and



are as defined in Claim 1 and R⁵ is as defined in Claim 2. 8. A compound represented by the general formula (Id),

wherein R1, R2, R3, A and

are as defined in Claim 1 and R⁵ is as defined in Claim 2.
9. A compound represented by the general formula (Ie),

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wherein R1, R2, R3, A and

are as defined in Claim 1 and R5 is as defined in Claim 2.

10. A compound according to Claim 9, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R2 and R3 are individually a hydrogen atom or an alkyl group.

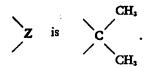
11. A compound according to Claim 5, wherein

12. A compound according to Claim 6, wherein

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13. A compound according to Claim 7, wherein

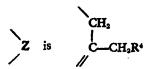
14. A compound according to Claim 8, wherein



15 15. A compound according to Claim 9, wherein

CH₃

16. A compound according to Claim 9, wherein



in which R4 is as defined above.

17. A compound according to Claim 1, wherein R1 is a hydrogen atom.

18. A compound according to Claim 1, wherein R1 is selected from ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed owing to enzymes in a living body.

19. A compound selected from

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TON	33.0000	
	$6 - [D(-) - \alpha - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)$ phenylacet-	
•	amido] penicillanic acid, $6 - [D(-) - \alpha - (4 - dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)-$	£
	phenylacetamido penicillanic acid, $6 - [D(-) - \alpha - (4 - enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	5
5	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	٠.
•	amino) phenylacetamido) penicillanic acid.	
10	$6 - [D(-) - \alpha - (4 - acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	10
10	$6 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - n - hexyl - 2 - oxo - 1 - piperazinocarbonylamino)pnenyl-$	
15	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	15
13	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonyl-$	
	amino \nhenvlacetamido nenicillanic acid.	
20	$6 - [D(-) - \alpha - (4 - n - octyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] penicillanic acid,$	20
-	$6 - [D(-) - \alpha - (4 - pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	
	$6 - [D(-)] - \alpha - (4 - palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
25	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{capryloyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenyl-	25 =
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - caproyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid, 6 - [D(-) - α - (4 - chloroacetyl - 2 - οχο - 1 - piperazinocarbonylamino) phenyl-	7
30	acetamido I renicillanic, acid.	30
	$6 - [D(-) - \alpha - (4 - benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido)penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - p - \text{chlorobenzoyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	
35	$6 - [D(-) - \alpha - (4 - p - methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonyl-$	35
	amino)phenylacetamido]penicillanic acid, 6 - $\{D(-) - \alpha - [4 - (3,4,5 - trimethoxybenzoyl) - 2 - oxo - 1 - piperazino-$	
	carbonylamino] phenylacetamido) penicillanic acid, $6 - \{D(-) - \alpha - [4 - (2,4 - dichlorobenzoyl) - 2 - oxo - 1 - piperazinocarbonyl-$	
40	amino] phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	40
	amino) nhenylacetamido) nenicillanic acid.	
	$6 - [D(-) - \alpha - (4 - phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid, and$	45
45	$6 - [D(-) - \alpha - (4 - \text{ethoxycarbonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) - phenylacetamido] penicillanic acid.$	45
	20 A compound selected from	
	6 - $[D(-) - \alpha - (4 - \text{methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	50
50	6 - $[D(-) - \alpha - (4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido) penicillanic acid,$	50
	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
	amido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - isopropyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	55
55	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - pentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	33 ,
	acetamido]pènicillanic àcid, 6 - [D() - α - (4 - iso - pentyl - 3 - οκο - 1 - piperazinocarbonylamino)phenyl-	
	acetamidol nenicillanic, acid.	60
60	$6 - [D(-) - \alpha - (2 - methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - n - butyl - 5 - methyl - 3 - oxo - 1 - piperazinocaroonyl-$	
	$6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	65
65	amino)phenylacetamido]penicillanic acid,	

161	1,508,062	161
	6 - $[D(-) - \alpha - (4 - benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	-
-	6 - $[D(-) - \alpha - (4 - \beta - \text{hydroxyethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] penicillanic acid,	-
5	$6 - [D(-) - \alpha - (4 - acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	5
•	$6 - [D(-) - \alpha - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	
	amino)phenylacetamido]penicillanic acid, 6 - [D(-) - α - (3 - οχο - 1 - piperazinocarbonylamino)phenylacetamido]peni-	
10	cillanic acid, $6 - [D(-) - \alpha - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$	10
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
15	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (2 - \text{ethoxycarbonylmethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonyl}$	15
13	amino)phenylacetamido]penicillanic acid,	15
	6 - $[D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	
20	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] penicillanic acid,	20
	$6 - [D(-) - \alpha - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido penicillanic acid.$	
	6 - [D(-) - α - (4 - α - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,	•
25	$6 - [D(-) - \alpha - (4 - \beta - \text{methylallyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	25
	phenylacetamido] penicillanic acid, $6 - \{D(-) - \alpha - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonyl-$	
•	amino]phenylacetamido}penicillanic acid, $6 - [D(-) - \alpha - (4 - n - \text{hexyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})\text{phenyl}$	
30	acetamido] penicillanic acid. $6 - [D(-) - \alpha - (4 - n - heptyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	30
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
4.	acetamido] penicillanic acid,	
35	6 - $[D(-) - \alpha - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	35
	6 - $[D(-) - \alpha - (4 - \text{cyclopentyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	
40	6 - $[D(-) - \alpha - (4 - phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	40
70	$6 - [D(-) - \alpha - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$	40
	acetamido] penicillanic acid, and $6 - [D(-) - \alpha - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
45	phenylacetamido]penicillanic acid. 21. A compound selected from	45
	$6 - [D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	
	$6 - [\hat{D}(-) - \alpha - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
50	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	50
	acetamido] penicillanic acid, and $6 - [D(-) - \alpha - (4 - benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido]penicillanic acid. 22. A compound selected from	
55	6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid,	55
	$6 - [\widetilde{D}(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
60	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	60
	phenylacetamido] penicillànic acid, $6 - [D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	
	phenylacetamido] penicillanic acid,	

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	6 - [D(-) - α - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] penicillanic acid,	
	$6 - [D(-) - \alpha - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
5	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	5
	acetamido] penicillanic acid, $6 - \{D(-) - \alpha - (4 - \beta - \text{chloroethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}\}$	*
	phenylacetamidó] penicillanic acid, $6 - [D(-) - \alpha - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	
10	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	10
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamidol penicillanic acid.	15
15	\cdot 6 - [D(-) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicilianic acid,	15
	$6 - [D(-) - \alpha - (4 - n - \text{heptyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
20	$6 - [D(-) - \alpha - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)$	20
20	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinothiocarbonylamino})$	
	phenylacetamido] penicillanic acid, 6 - $[D(-)$ - α - $(4$ - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-	
. 25	hydroxyphenylacetamido penicillanic acid, 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p$	25
23	hydroxyphenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-$	
	cyclohexadienylacetamido] penicillanic acid, 6 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-	,
30	cyclohevodienylacetamidol nenicillanic, acid.	30
-	$6 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienylacetamido] penicillanic acid,$	
	6 - $[D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido] penicillanic acid,$	
35	6 - [DL - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-	35
	6 - [DL - a - (4 - ethyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienyl-acetamido penicillanic acid,	
40	$6 - [DL - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperadinocarbonylamino) - 2-$	40
40	thienylacetamido] penicillanic acid, and 6 - [DL - 12 - (4 - 11 - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-	10
	thienylacetamido]penicillanic acid. 23. A compound selected from	
45	$6 - [D(-) - \alpha - (2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-amino phenylacetamido penicillanic acid.$. 45
45	$6 - [D(-) - \alpha - (3.5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido]-penicillanic acid,	
	$6 - [D(-) - \alpha - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonyl-$	
50	amino) phenylacetamido) penicillanic acid, $6 - [D(-) - \alpha - (4 - benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazino-$	50
	carbonylamino) phenylacetamido penicillanic acid, $6 - [D(-) - \alpha - (4 - \beta_1\beta_2\beta - trichloroethoxycarbonyl - 2,2 - pentamethylene-$	
	3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, and 6 - [D(-) - α - (4 - benzyl - 2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piper-	
55	azinocarbonylamino)phenylacetamido]penicillanic acid. 24. A compound selected from	55
	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - methyl - \Delta^3 - cephem - 4 - carboxylic acid,$	
	$7 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonyiamino})$ pnenyi-	60
60	acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	60 .
	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4$ - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	
65	acetamido $\bar{\ \ }$ - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $\bar{\ \ }$ D(-) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	65
55	· L= V / · · · · · · · · · · · · · · · · · ·	

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5		phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	· · · · · · · · · · · · · · · · · · ·
•	- 5	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	. 5
1		7 - $[D(-)$ - α - $(4 - n - \text{octyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid.	3
	10	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - \Delta^3 - cephem - 4 - carboxylic acid.$	10
	10	7 - $[D(-)$ - α - $(4 - n$ - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4$ - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	10
	15	acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothicarbonylamino)	15
		phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,	-
	20	7 - $[D(-)$ - α - $(4$ - methyl - $2,3$ - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,	20
1	- 25	7 - $[D(-)$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,	-25
:	_	7 - $[D(-)$ - α - $(4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^0-cephem - 4 - carboxylic acid,$	
	30	7 - $[D(-)$ - α - $(4$ - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - $[2$ - $(5$ - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 -cephem - 4 - carboxylic acid,	30
		7 - $[D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem-4 - carboxylic acid,$	
	35	7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^a - cephem-4 - carboxylic acid,	35
	40	7 - $[D(-)$ - α - $(4$ - ethyl - 6 - methyl - $2,3$ - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5$ - $(1$ - methyl - $1,2,3,4$ - tetrazolyl) - thiomethyl]- Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4,6$ - dimethyl - $2,3$ - dioxo - 1 - piperazinocarbonylamino)-	40
		phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ ³ -cephem - 4 - carboxylic acid,	
	45	7 - $[D(-)$ - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^0 - cephem-4 - carboxylic acid,	45
		7 - [$D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	
	50	7 - [D() - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	50
•	55	7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	55
٠		7 - $[D(-)$ - α - $(4$ - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(1$ - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	33
(60	7 - $[D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - \Delta^a - cephem - 4-carboxylic acid,$	60
		7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p-$	

164	1,508,062	164
	hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]- Δ^{g} - cephem - 4 - carboxylic acid,	
5	7- $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - azidomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl})$ - thiomethyl] - Δ^3 - cephem 4 - carboxylic acid,	5
10	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1, 2, 3, 4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem-4 - carboxylic acid,7 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenyl-$	10
	acetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic	
15	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^0 - cephem - 4 - carboxylic acid,$	15
20	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacid,	20
	acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [3 - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl)-	
25	thiomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (4 - methyloxazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	25 ❤
30	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (4 - methylthiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	30
	acetamido] - 3 - [2 - (pyridyl - 1 - oxide) - thiomethyl] - Δ ^a - cephem - 4 - carboxylic	35
35	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - thiazolinylthiomethyl) - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methylimidazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic	33
40	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - pyrimidinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (6 - methylpyridazinyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid, \Delta^3$	40
45	boxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [1 - (4 - methylpiperazino) - thiocarbonylthiomethyl] - Δ^3 - cephem-4 - carboxylic acid,	45
50	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{diox} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[5 - (3 - \text{methylisoxazolyl}) - \text{carbonylthiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid, 7 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{diox} - 1 - \text{piperazinocarbonylamino}) phenyl-$	50
	acetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^a - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamidol - 3 - pyridinomethyl - Δ^a - cephem - 4 - carboxylic acid betaine, and	
55 .	7 - $[D(-)$ - α - $(4$ - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - pyridinomethyl - α - cephem - 4 - carboxylic acid betaine. 25. A compound selected from 7 - $[D(-)$ - α - $(4$ - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-	55
. 60	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4- thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-	60
65	carboxylic acid, $7 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino) - acid$	65

	, ,	
,	phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^0 -cephem - 4 - carboxylic acid,	
2	7 - $[D(-)$ - α - $(4$ - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^{α} - cephem-	
5	4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	5
ā	amido] - $3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid,$	
10	7 - $[D(-)$ - α - $(4$ - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	10
	7 - [D(-) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	
15	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^B - cephem - 4-carboxylic acid,$	15
20	7 - $[D(-)$ - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-3 - $[2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid,$	20
20	7 - [D(-) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,	-
້ 25	7 - [D($-$) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid.	25
	7 - $[D(-)$ - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 -	
30	cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	30
30	amido] - $3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,7 - [D(-) - \alpha - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	
35	amido] - $\ddot{3}$ - $[\ddot{5}$ - $(1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	35
	7 - $[D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid,$	
40	7 - $[D(-) - \alpha - (4 - \text{methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazoiyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	40
	7 - $[D(-)$ - α - $(4$ - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5$ - $(1$ - methyl-1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	
45	7 - $[D(-) - \alpha - (3.5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - [5 - (1 - \text{methyl} - 1.2.3.4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4 - carboxylic acid, and$	45
	7 - $[D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
50	acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ ⁰ - cephem-4 - carboxylic acid. 26. A compound selected from	50
-	pivaloyloxymethyl 6 - $[D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanate,phthalidyl 6 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	
[•] 55	amino)phenylacetamido)penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl}-$	55
	amino)phenylacetamido]penicillanate, phthalidyl 6 - $[D(-)$ - α - $(4$ - iso - propyl - 2,3 - dioxo - 1 - piperazinocar-	
60	bonylamino)phenylacetamido]penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	60
υυ	amino)phenylacetamido]penicillanate, methoxymethyl 6 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino-	
	carbonylamino)phenylacetamido]penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl}-$	
65	amino)phenylacetamido]penicillanate,	65

166	1,508,062	166
	methoxymethyl 6 - $[D(-)$ - α - $(4 - n$ - butyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido)penicillanate, methoxymethyl 6 - $[D(-)$ - α - $(4$ - iso - propyl - 2,3 - dioxo - 1 - piperazino-	
5	carbonylamino)phenylacetamido]penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate,pivaloyloxymethyl 6 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	5
10	carbonylamino)phenylacetamido]penicillanate, pivaloyloxymethyl 6 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazino- carbonylamino)phenylacetamido]penicillanate, pivaloyloxymethyl 6 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino- carbonylamino)phenylacetamido]penicillanate,	10
15	β - piperidinoethyl 6 - $[D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate, \beta - piperidinoethyl 6 - [D(-) - \alpha - (4 - n - octyl - 2, 3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate, \beta - morpholinoethyl 6 - [D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazino-$	15
20	carbonylamino)phenylacetamido]penicillanate, β - morpholinoethyl 6 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino- carbonylamino)phenylacetamido]penicillanate, and methoxymethyl 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino- carbonylamino)phenylacetamido] - 3 - methyl - Δ³ - cephem - 4 - carboxylate.	20
25	 27. A compound according to Claim 1, 5, 6, 7, 8 or 9, wherein R¹ is a cation capable of forming a non-toxic salt. 28. A non-toxic salt of a compound according to Claim 19, 20, 21, 22, 23, 24 or 25. 29. 6 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- 	25
30	phenylacetamido] penicillanic acid or its non-toxic salt. 30. $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] penicillanic acid or its non-toxic salt. 31. $6 - [D(-) - \alpha - (6 - \text{methyl} - 4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl-amino})$ phenylacetamido] penicillanic acid or its non-toxic salt.	30
35 -	32. $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p-hydroxyphenylacetamido] penicillanic acid or its non-toxic salt. 33. 7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})- phenylacetamido] - 3 - [5 - (1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid or its non-toxic salt.$	35
40	34. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3-cephem - 4 - carboxylic acid or its non-toxic salt. 35. 7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3-$	40
45	cephem - 4 - carboxylic acid or its non-toxic salt. 36. $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - $3 - [2 - (1 - \text{methyl} - 1,3,4 - \text{triazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem- 4 - carboxylic acid or its non-toxic salt. 37. 7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})-$	45
50	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt. 38. 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-p - hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt. 39. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	50
55	phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^{0} - cephem - 4 - carboxylic acid or its non-toxic salt. 40. A process for producing a compound represented by the general formula (I),	55

$$A - N = 0$$

$$(R^2 R^3)_{m}$$

$$(R^2 R^3)_{m}$$

$$(R^2 R^3)_{m}$$

$$(R^2 R^3)_{m}$$

$$(R^2 R^3)_{m}$$

$$(R^2 R^3)_{m}$$

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=10

5

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wherein R, A, X, n, m, R₁, R₂, R₃, Y and Z are as herein defined which comprises reacting a compound represented by the general formula (II),

wherein R' represents a hydrogen atom, a silicon or phosphorous containing group, which is capable of easy removal by treatment with water or an alcohol; R, R¹ and

z

are as defined above, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III),

$$A - N = C - OH$$
 (111)

wherein A, X, Y, R², R³, n and m are as defined above.
41. A process for producing a compound represented by the general formula (I),

$$A - N = \begin{cases} X \\ 3 \\ 2 \\ 1 \end{cases}$$

$$A - N = \begin{cases} X \\ 3 \\ 2 \\ 1 \end{cases}$$

$$A - N = \begin{cases} X \\ 3 \\ 2 \\ 1 \end{cases}$$

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$$A - N = \begin{cases} X \\ 3 \end{cases}$$

$$A - N = \begin{cases} X \\ 3 \end{cases}$$

$$A - N = \begin{cases} X \\ 3 \end{cases}$$

wherein A, Y, R, R1, R2, R3, X,

Z,

n and m are as defined in Claim 40, which comprises reacting a compound represented by the general formula (IV),

S (1V)

wherein R1, R' and

z

are as defined in Claim 40, with a compound represented by the general formula (V),

$$\begin{array}{c} (X)_{n} \\ A - N \\ (R^{2} R^{3})_{m} \end{array} = \begin{array}{c} C - NH - R - C - OH \\ 0 \end{array}$$
 (V)

wherein A, R, R², R³, X, Y, n and m are as defined in Claim 40, or with a reactive derivative in the carboxyl group of the compound of formula (V).

42. A process for producing a compound represented by the general formula (I'),

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$$A - N = \begin{pmatrix} X \\ N \end{pmatrix}_{m} - C - NH - R - CONH - CH_{2}R^{4\alpha}$$

$$(11)$$

$$(R^{2} R^{3})_{m}$$

$$(11)$$

wherein A, R, R¹, R², R³, X, Y, n and m are as defined in Claim 1 and R⁴ⁿ represents a cyano group, an azido group, a quaternary ammonium group, or a substituted or unsubstituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, arylthiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio, or heterocyclylthio group, which comprises reacting a compound represented by the general formula (VI),

$$A - N = C - NH - R - CONH$$

$$(VI)$$

$$(R^2 R^3)_{m}$$

$$(VI)$$

wherein B represents a substituent capable of being easily replaced by a nucleophilic reagent; and A, R, R¹, R², R³, X, Y, n and m are as defined in Claim 40, with a compound represented by the general formula (VII),

 R^8M (VII)

wherein M represents a hydrogen atom, or an alkali metal or alkaline earth metal atom; and R^a represents a cyano group, an azido group or an organic group linked through O, N or S, or with a tertiary amine.

43. A process according to Claim 40, 41 or 42, wherein R is a group represented by the formula,

in which R⁵ is as defined in claim 2.

44. A process according to Claim 40 or 41, wherein

45. A process according to Claim 40 or 41, wherein

in which R⁴ is as defined in Claim 40.
46. A process according to Claim 40 or 41, wherein R is

in which R^5 is as defined in Claim 43, n is 1, m is 3, and X is an oxygen atom linked to the carbon atom at the 2-position of the piperazine ring.

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47. A process according to Claim 40 or 41, wherein R is

in which R^s is as defined in Claim 43, n is 1, m is 3 and X is an oxygen atom linked to the carbon atom at the 3-position of the piperazine ring.

48. A process according to Claim 40 or 41, wherein R is

--CH---| | Ba

in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 5-positions of the piperazine ring.

49. A process according to Claim 40 or 41, wherein R is

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in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms

linked to the carbon atoms at the 3- and 5-positions of the piperazine ring.

50. A process according to Claim 40 or 41, wherein R is

in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

51. A process according to Claim 42 or 45, wherein R is

in which R⁵ is as defined in Claim 43; n is 2; m is 2; and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

52. A process according to Claim 46, wherein

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53. A process according to Claim 47, wherein

54. A process according to Claim 48, wherein

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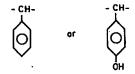
25

55. A process according to Claim 49, wherein

56. A process according to Claim 50, wherein

57. A process according to Claim 40, 41 or 42, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R² and R⁰ are individually a hydrogen atom or an alkyl group.

58. A process according to Claim 40 or 41, wherein R is



n is 2; m is 2 and two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring, each pair of R² and R³, which may be the same or different, are individually a hydrogen atom or a methyl group, A is a methyl or ethyl group, R¹ is a hydrogen atom or a cation capable of forming a non-toxic salt and

in which R⁴ is an acetoxy, 5 - (2 - methyl - 1,3,4 - thiadiazolyl) - thio, 5 - (1,3,4-thiadiazolyl) - thio, 2 - (1 - methyl - 1,3,4 - triazolyl) - thio, 5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thio or 5 - (1,2,3,4 - tetrazolyl) - thio group.

59. A process according to Claim 42, wherein R is



n is 2, m is 2; two X's are oxygen atoms linked to the carbon atoms at the 2- and 3positions of the piperazine ring; each pair of R² and R³, which may be the same or
different, are individually a hydrogen atom or methyl group; A is a methyl or ethyl
group; and R¹ is a hydrogen atom or a cation capable of forming a non-toxic salt.

60. A process according to Claim 42, wherein \mathbb{R}^4 and \mathbb{R}^8 are the same and selected from, 5-(2-methyl-1,3,4-thiadiazolyl)-thio, 5-(1,3,4-thiadiazolyl)-thio, 5-(1-methyl-1,2,3,4-tetrazolyl)-thio, and 5-(1,2,3,4-tetrazolyl)-thio groups.

61. A process according to Claim 40 or 41, wherein R' is a hydrogen atom.
62. A process according to Claim 40, 41 or 42, wherein R¹ is a cation capable of

forming a salt.

63. A process according to Claim 62, wherein the salt is a non-toxic salt.

64. A process according to Claim 40, 41 or 42 wherein R¹ is selected from the

17:1	1,508,062	171		
5	group consisting of ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed owing to enzymes in a living body. 65. A process according to Claim 40 or 41, wherein R ¹ is a trialkylammonium. 66. A process according to Claim 40, wherein the reactive derivative in the (thio)-carboxyl group of a compound of formula (III) is an acid halide. 67. A process according to Claim 41, wherein the reactive derivative in the carboxyl	5		
10	group of a compound of formula (V) is a mixed acid anhydride. 68. A process according to Claim 40 or 41, wherein the reaction is carried out in the presence of an acid-binding agent. 69. A process according to Claim 41, wherein the reaction is carried out in the			
15	presence of a dehydrating condensing agent. 70. A process according to Claim 40 or 41, wherein at least one of R ² and R' is a silicon, or a phosphorus containing group capable of easy removal by treatment with water or an alcohol.	15		
20	 71. A process according to Claim 40 or 41, wherein the reaction is carried out at a temperature of -60° to +80°C. 72. A process according to Claim 42, wherein B is a halo-substituted or unsubstituted lower alkanoyloxy group. 			
20	73. A process according to Claim 42, wherein B is an acetoxy group. 74. A process according to Claim 42, wherein R ^a is an organic group linked through O or S. 75. A process according to Claim 42, wherein the compound (VII) is selected	20		
ģ	from			
~2 5	N-N	25		
	CH ₃ O SH, CH ₃ CH ₃ CH ₃ CH ₃ N C			
	CH ₃ N SH, NaN ₃ , CH ₃ N			
	CH_3 $C-SNa$, $C_2H_5O-C-SNa$, and CH_3OH .			
-	Ö "S"			
*30	 76. A process according to Claim 42, wherein the tertiary amine is pyridine. 77. A process according to Claim 42, wherein the reaction is carried out in a polar solvent at a pH of 2 to 10. 78. A process according to Claim 42, wherein the reaction is carried out at a tem- 	30		

78. A process according to Claim 42, wherein the reaction is carried out at a temperature of 0° to 100°C.

79. A process according to Claim 42, wherein B is a hetero aromatic amine N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide in the molecule, and the reaction is effected in the presence of a cupric compound.

80. A pharmaceutical composition containing as an active ingredient the compound as claimed in Claim 1.

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